Hand-Carried to:	**Office of Patent Legal Administration** **Room MDW 7D55** **600 Dulany Street (Madison Building)** **Alexandria, VA 22314**

PATENT
Attorney Docket No. P-088-US1
Customer No. 27038

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Michael R. Leadbetter et al.	)	Confirmation No. 5218
	)	
U.S. Patent No. 6,635,618 B2	)	
	)	
Issued: October 21, 2003	)	
	)	
Application No. 09/847,042	)	
	)	
Filed: May 1, 2001	)	
	)	
For: GLYCOPEPTIDE PHOSPHONATE DERIVATIVES	)	
	)	

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is an application for extension of the patent term of U.S. Patent No. 6,635,618 B2 under 35 U.S.C. § 156. Two additional copies of this submission are also enclosed.

The Director is hereby authorized to charge the requisite fee set forth in 37 C.F.R. § 1.20(j)(1) (i.e., $1,120.00) and any other fees required by this application to Deposit Account No. 50-0344, in the name of Theravance, Inc.

Respectfully submitted,

THERAVANCE, INC.

Date: Oct. 13, 2009

By: _____
Jeffrey A. Hagenah, Ph.D.
Reg. No. 35,175
(650) 808-6406

THERAVANCE, INC.
901 Gateway Blvd.
South San Francisco, CA 94080
(650) 808-6000
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Enclosures:

Postcard

Transmittal Letter (2 pages)

Application for Patent Term Extension (17 pages) (original + 2 copies)

Appendix A – Copy of Approval Letter (w/Appendix A Cover Page) (43 pages) (original + 2 copies)

Appendix B – Copy of U.S Patent 6,635,618 B2 (w/Appendix B Cover Page) (29 pages) (original + 2 copies)

Appendix C – Copy of Related Documents (w/Appendix C Cover Page) (4 pages) (original + 2 copies)

Appendix D – Brief Description of Activities (w/ Appendix D Cover Page) (25 pages) (original + 2 copies)

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For: GLYCOPEPTIDE PHOSPHONATE DERIVATIVES	)	

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant (Theravance, Inc.) hereby requests that the term of U.S. Patent No. 6,635,618 B2 be extended for the full period permitted under 35 U.S.C. § 156.

I. OWNER OF RECORD

Applicant is the assignee of the entire right, title and interest in U.S. Patent No. 6,635,618 B2, granted on October 21, 2003, by virtue of an assignment from the inventors to Advanced Medicine, Inc. recorded on August 6, 2001 in the United States Patent and Trademark Office at Reel 012049, Frame 0333; and a merger (name change) of Advanced Medicine, Inc. to Theravance, Inc. recorded on June 14, 2002 in the United States Patent and Trademark Office at Reel 013003, Frame 0075.

II. INFORMATION TO DETERMINE ELIGIBILITY OF PATENT FOR EXTENSION

Pursuant to 35 U.S.C. § 156, Applicant submits the following information required under 37 C.F.R. § 1.740 to identify the approved product and the patent; and to enable the Director to determine the eligibility of this patent for extension of the patent term.

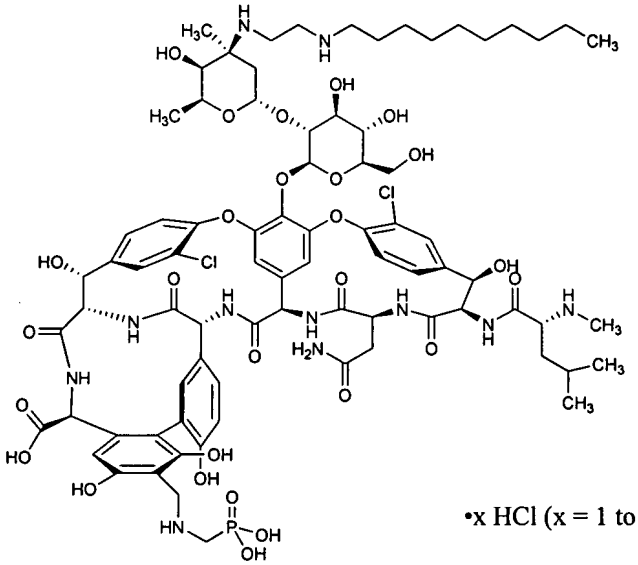
(1) Complete Identification of the Approved Product – § 1.740(a)(1)

The approved product is VIBATIV™ (telavancin) for injection, 250 mg and 750 mg. The approved product is identified by generic name, chemical name and chemical structure as follows:

(a) Generic Name: telavancin hydrochloride

(b) Chemical Name: Vancomycin, *N3''*-[2-(decylamino)ethyl-29-[(phosphonomethyl)amino]methyl]-, hydrochloride

(c) Chemical Structure:



(2) Complete Identification of Federal Review Statute – § 1.740(a)(2)

The approved product was subject to regulatory review under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355), as a human drug.

(3) Identification of Date of Approval – § 1.740(a)(3)

The approved product received permission for commercial marketing or use under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) on September 11, 2009. A copy of the approval letter is attached as APPENDIX A.

(4) Identification of Active Ingredient – § 1.740(a)(4)

The active ingredient in the approved product is telavancin hydrochloride. The active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) Statement that Application is Being Submitted within Sixty-Day Period for Submission – § 1.740(a)(5)

This application for extension of patent term is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), which period expires on November 9, 2009 (i.e., the last day on which the application can be submitted).

(6) Complete Identification of the Patent – § 1.740(a)(6)

The patent for which patent term extension is being sought is identified as follows:

(a) Inventors: Michael R. Leadbetter and Martin S. Linsell

(b) U.S. Patent No.: 6,635,618 B2

(c) Issue Date: October 21, 2003

(d) Expiration Date (unless extended): September 22, 2021

(7) Copy of Patent – § 1.740(a)(7)

A copy of the patent is attached as APPENDIX B, including the entire specification and claims. This patent has no drawings.

(8) Copies of Related Documents – § 1.740(a)(7)

Copies of the following documents issued for the patent are attached as APPENDIX C:

(a) Certificate of correction signed and sealed on June 8, 2004;

(b) Certificate of correction signed and sealed on November 1, 2005; and

(c) Maintenance Fee Statement dated May 1, 2007.

(9) Statement that Patent Claims Approval Product, Etc. – § 1.740(a)(9)

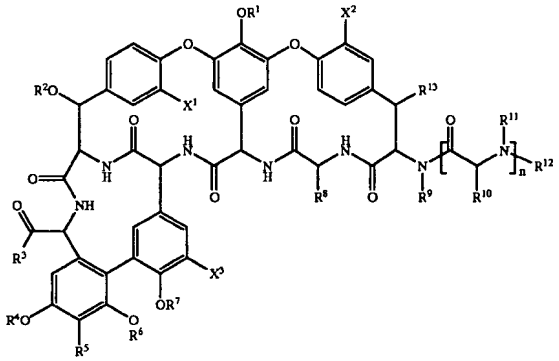
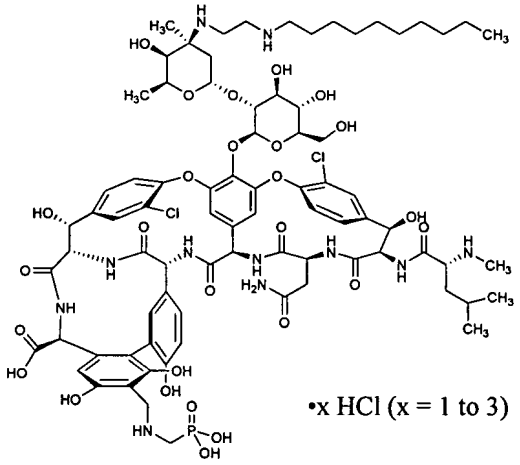
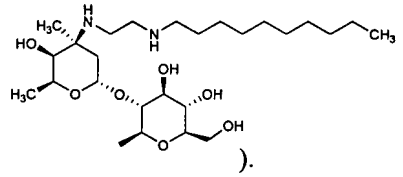
U.S. Patent No. 6,635,618 B2 claims the approved product, or a method of using or manufacturing the approved product. The applicable patent claims are Claims 1, 3-9, 12-15, 18-27, and 29-31. As required by 37 C.F.R. §1.740(a)(9), the following table demonstrates the manner in which at least one such claim reads on:

(a) the approved product (Claims 1, 5, 14 and 20 used as representative examples) (§ 1.740(a)(9)(i));

(b) the method of using the approved product (Claim 30 used as a representative example) (§ 1.740(a)(9)(ii)); and

(c) the method of manufacturing the approved product (Claim 29 used as a representative example) (§ 1.740(a)(9)(iii)).

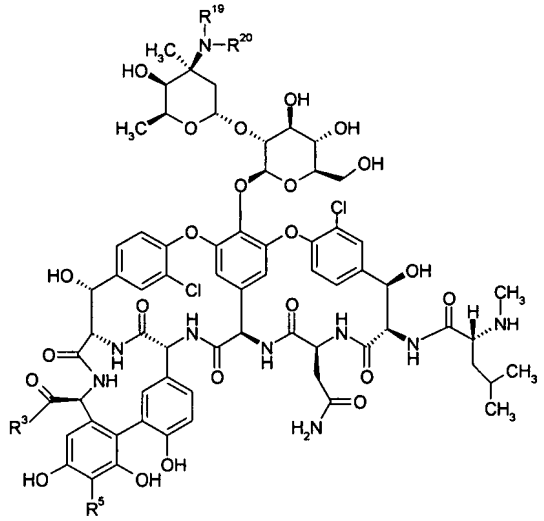
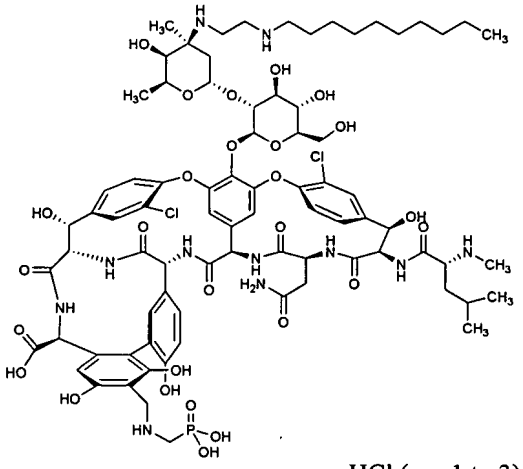
Claim	Approved Product, Etc.
1. A glycopeptide substituted with one or more substituents each comprising one or more phosphono groups; or a pharmaceutically acceptable salt, or stereoisomer, or prodrug thereof.	The approved product contains telavancin hydrochloride which is a pharmaceutically acceptable salt of a glycopeptide substituted with a substituent comprising a phosphono group (i.e., $-CH_2-NH-CH_2-P(O)(OH)_2$).

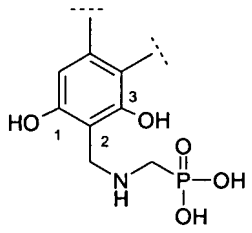
Claim	Approved Product, Etc.
5. A glycopeptide of formula I: 	The approved product contains telavancin hydrochloride which is a glycopeptide of the formula:  •x HCl (x = 1 to 3)
wherein:	Telavancin hydrochloride corresponds with the variables in formula I of Claim 5 as follows:
R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-R^a-Y-R^b-(Z)_x$; or R^1 is a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$, R^f, $-C(O)R^f$, or $-C(O)-R^a-Y-R^b-(Z)^x$;	R^1 is a saccharide group substituted with $-R^a-Y-R^b-(Z)_x$ (i.e., a group of the formula: ).
R^2 is hydrogen or a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$, R^f, $-C(O)R^f$, or $-C(O)-R^a-Y-R^b-(Z)_x$;	R^2 is hydrogen;
R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^e$, or $-O--R^e$; or R^3 is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups;	R^3 is $-OR^c$ (i.e., -OH);
R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, $-C(O)R^d$ and a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$, R^f, $-C(O)R^f$, or $-C(O)-R^a-Y-R^b-(Z)_x$, or R^4 and R^5 can be joined, together with the atoms to which they are attached, to form a heterocyclic ring optionally substituted with $-NR^c-R^a-Y-R^b-(Z)_x$;	R^4 is hydrogen;

Claim	Approved Product, Etc.
R^5 is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$, $-CH(R^c)-NR^cR^e$, $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x$, $-CH(R^c)-R^x$, $-CH(R^c)-NR^c-R^a-C(=O)-R^x$, and a substituent that comprises one or more phosphono groups;	R^5 is a substituent that comprises one phosphono group (i.e., $-CH_2-NH-CH_2-P(O)(OH)_2$);
R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, $-C(O)R^d$ and a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$, R^f, $-C(O)R^f$, or $-C(O)-R^a-Y-R^b-(Z)_x$, or R^5 and R^6 can be joined, together with the atoms to which they are attached, to form a heterocyclic ring optionally substituted with $-NR^c-R^a-Y-R^b-(Z)_x$;	R^6 is hydrogen;
R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, and $-C(O)R^d$;	R^7 is hydrogen;
R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;	R^8 is substituted alkyl (i.e., $-CH_2-C(O)NH_2$);
R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;	R^9 is hydrogen;
R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $-Ar^1-O-Ar^2-$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;	R^{10} is alkyl (i.e., $-CH_2CH(CH_3)_2$);
R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and	R^{11} is alkyl (i.e., $-CH_3$);

Claim	Approved Product, Etc.
heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;	
R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, $-C(NH)NR^cR^c$, $-R^a-Y-R^b-(Z)_x$, and $-C(O)-R^a-Y-R^b-(Z)_x$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;	R^{12} is hydrogen;
R^{13} is selected from the group consisting of hydrogen or $-OR^{14}$;	R^{13} is $-OR^{14}$ (i.e., -OH);
R^{14} is selected from hydrogen, $-C(O)R^d$ and a saccharide group;	R^{14} is hydrogen;
each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;	R^a is alkylene (i.e., $-CH_2CH_2-$);
each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;	R^b is alkylene (i.e., $-(CH_2)_{10}-$);
each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;	each R^c is hydrogen;
each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;	R^d is not present;
R^e is a saccharide group;	R^e is not present;

Claim	Approved Product, Etc.
each R^f is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, or heterocyclic;	R^f is not present;
R^x is an N-linked amino saccharide or an N-linked heterocycle;	R^x is not present;
X^1, X^2 and X^3 are independently selected from hydrogen or chloro;	X^1 is chloro; X^2 is chloro; X^3 is hydrogen;
each Y is independently selected from the group consisting of oxygen, sulfur, -S-S-, -NR^c-, -S(O)-, -SO_2-, -$NR^cC(O)$-, -OSO_2-, -OC(O)-, -NR^cSO_2-, -$C(O)NR^c$-, -C(O)O-, -SO_2NR^c, -SO_2O-, -$P(O)(OR^c)O$-, -$P(O)(OR^c)NR^c$-, -$OP(O)(OR^c)O$-, -$OP(O)(OR^c)NR^c$-, -$OC(O)O$-, -$NR^cC(O)O$-, -NR^c $C(O)NR^c$-, -$OC(O)NR^c$-, -C(=O)-, and -NR^cSO_2 NR^c-;	Y is -NR^c- (i.e, -NH-);
each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;	Z is hydrogen;
n is 0, 1 or 2; and	n is 1;
x is 1 or 2;	x is 1;
or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof;	a pharmaceutically acceptable salt (i.e., a hydrochloride salt);
provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.	R^5 is a substituent comprising one phosphono group (i.e., -CH_2-NH-CH_2-$P(O)(OH)_2$).

Claim	Approved Product, Etc.
14. The glycopeptide of claim 5 which is a compound of formula II: 	The approved product contains telavancin hydrochloride which is a glycopeptide of the formula:  •x HCl (x = 1 to 3)
wherein:	Telavancin hydrochloride corresponds with the variables in formula II of Claim 14 as follows:
R^{19} is hydrogen;	R^{19} is hydrogen;
R^{20} is $-R^a$-Y-R^b-$(Z)_x$, R^f, -C(O)R^f, or -C(O)-R^a-Y-R^b-$(Z)^x$;	R^{20} is $-R^a$-Y-R^b-$(Z)_x$ (i.e., $-CH_2CH_2$-NH-$(CH_2)_9CH_3$);
R^a, Y, R^b, Z, x, R^f, R^3 and R^5 have the values defined in claim 5;	R^a, Y, R^b, Z, x, R^f, R^3 and R^5 have the values defined in claim 5; (i.e., R^a is $-CH_2CH_2-$; Y is -NH-; R^b is $-(CH_2)_{10}-$; Z is hydrogen; x is 1; R^f is not present; R^3 is –OH and R^5 is a substituent comprising one phosphono group (i.e., $-CH_2$-NH-CH_2-P(O)$(OH)_2$).
or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof;	a pharmaceutically acceptable salt (i.e., a hydrochloride salt);
provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.	R^5 is a substituent comprising one phosphono group (i.e., $-CH_2$-NH-CH_2-P(O)$(OH)_2$).

Claim	Approved Product, Etc.
20. The glycopeptide of claim 14 wherein R^3 is –OH; R^5 is N-(phosphomethyl)aminomethyl; R^{19} is hydrogen, and R^{20} is $-CH_2CH_2$-NH-$(CH_2)_9CH_3$; or a pharmaceutically acceptable salt thereof.	Telavancin hydrochloride is a glycopeptide of claim 14, that corresponds as follows: R^3 is –OH; R^5 is N-(phosphomethyl)aminomethyl (i.e., $-CH_2$-NH-CH_2-$P(O)(OH)_2$); R^{19} is hydrogen, and R^{20} is $-CH_2CH_2$-NH-$(CH_2)_9CH_3$; a pharmaceutically acceptable salt (i.e., a hydrochloride salt).
29. A method of preparing a glycopeptide of claim 3,* comprising derivatizing a corresponding starting glycopeptide wherein the 2-position of the 1,3-dihydroxyphenyl moiety is unsubstituted. *Claim 3 recites a glycopeptide comprising a 1,3-dihydroxyphenyl moiety, wherein the glycopeptide is substituted at the 2-position of the 1,3-dihydroxyphenyl moiety with a substituent comprising one or two phosphono groups.	Telavancin hydrochloride is prepared by derivatizing the corresponding starting glycopeptide wherein the 2-position of the 1,3-dihydroxyphenyl moiety is unsubstituted. Telavancin hydrochloride is a glycopeptide comprising a 1,3-dihydroxyphenyl moiety (i.e. a moiety of the formula:  that is substituted at the 2-position of the 1,3-dihydroxyphenyl moiety with a substituent comprising one phosphono group (i.e., $-CH_2$-NH-CH_2-$P(O)(OH)_2$).
30. A method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a therapeutically effective amount of a glycopeptide of any one of claims 1, 5, 14, or 20.	The approved product has been approved for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. Treatment involves administering 10 mg/kg over 60 minutes by intravenous infusion once every 24 hours for 7 to 14 days.

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(10) Statement of Relevant Dates and Information – § 1.740(a)(10)

To enable the Secretary of Health and Human Services to determine the applicable regulatory review period for this patent which claims a human drug, the following relevant dates and information pursuant to 35 U.S.C. § 156(g) are provided in the order specified in 37 C.F.R. § 1.740(a)(10)(i):

(a) Effective date of the IND application: **June 27, 2002** (i.e., 30 days after FDA receipt of the IND).

IND Number: **IND 60,237**.

(b) Date NDA was initially submitted: **December 7, 2006**.

NDA Number: **NDA 22-110**.

(c) Date NDA was approved: **September 11, 2009**.

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(11) Brief Description of Activities of Applicant During Regulatory Review Period – § 1.740(a)(11)

A brief description of the significant activities undertaken by Applicant during the applicable regulatory review period with respect to the approved product and the dates applicable to these significant activities is set forth in APPENDIX D.

(This Section to Begin on a New Page)

(12) Statement that Patent is Eligible for Extension – § 1.740(a)(12)

In the opinion of Applicant, U.S. Patent No. 6,635,618 B2 is eligible for extension of its patent term under 35 U.S.C. § 156 because this patent claims the approved product, a method of using the approved product or a method of manufacturing the approved product; and it satisfies all of the requirements for patent term extension as follows:

(a) as required by 35 U.S.C. § 156(a)(1), this application was submitted before expiration of the term of the patent;

(b) as required by 35 U.S.C. § 156(a)(2), the term of the patent has not been previously extended under 35 U.S.C. § 156(e)(1);

(c) as required by 35 U.S.C. § 156(a)(3), this application has been submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d);

(d) as required by 35 U.S.C. § 156(a)(4), the approved product was subject to a regulatory review period before its commercial marketing or use;

(e) as required by 35 U.S.C. § 156(a)(5)(A), the permission for commercial marketing or use of the approved product after the regulatory review period was the first permitted commercial marketing or use of the approved product under the provision of law under which such regulatory review period occurred; and

(f) as required by 35 U.S.C. § 156(c)(4), no other patent has been extended under 35 U.S.C. § 156(e)(1) for the same regulatory review period for the approved product.

(13) Statement as to the Length of Extension Claimed and How the Length Was Determined –§1.740(a)(12)

Applicant claims the length of patent term extension permitted by 35 U.S.C. § 156(c), i.e., extension of the patent term from September 22, 2021 to September 11, 2023, or 719 days. The length of patent term extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) Regulatory Review Period: Pursuant to 37 C.F.R. § 1.775(c), the length of the regulatory review period was determined as follows:

Calculation of Length of the Regulatory Review Period	
37 C.F.R. § 1.775(c)(1): The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product (i.e., **June 27, 2002**) and ending on the date an application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act (i.e., **December 7, 2006**)	**June 27, 2002 to December 7, 2006** **= 1624 days**
37 C.F.R. § 1.775(c)(2): The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act (i.e., **December 7, 2006**) and ending on the date such application was approved under such section (i.e., **September 11, 2009**)	**December 7, 2006 to September 11, 2009** **= 1009 days**
Length of the regulatory review period is sum of (c)(1) + (c)(2):	**2633 days**

(b) Patent Term Extension: Pursuant to 37 C.F.R. § 1.775(d), the length of the patent term extension was determined as follows:

Calculation of Length of Patent Term Extension	
37 C.F.R. § 1.775(d)(1): Number of days in regulatory review period	**2633 days**
37 C.F.R. § 1.775(d)(1)(i): Subtracting number of days in the periods of paragraphs (c)(1) and (c)(2) which were on or before the date on which the patent issued (i.e., from **June 27, 2002** to **October 21, 2003**)	**June 27, 2002 to October 21, 2003** **= 481 days**
Subtotal	**2152 days**
37 C.F.R. § 1.775(d)(1)(ii): Subtracting number of days in the periods of paragraphs (c)(1) and (c)(2) during which it is determined under 35 U.S.C. §156(d)(2)(B) that the applicant did not act with due diligence	**0 days**
Subtotal	**2152 days**
37 C.F.R. § 1.775(d)(1)(iii): Subtracting one-half the number of days remaining in the period defined by paragraph (c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) (ignoring half days)	**(1624 days - 481 days) / 2** **= 571 days**
Total Number of Days Under 37 C.F.R. § 1.775(d)(1)	**1581 days**
37 C.F.R. § 1.775(d)(2): Adding the number of days determined in paragraph (d)(1) to the original term of the patent (i.e. **September 22, 2021**) as shortened by any terminal disclaimer	**January 20, 2026**
37 C.F.R. § 1.775(d)(3): Adding 14 years to the date of the approval of the application (i.e., **September 11, 2009**) under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act	**September 11, 2023**
37 C.F.R. § 1.775(d)(4): Comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) with each other and selecting the earlier date	**September 11, 2023**
37 C.F.R. § 1.775(d)(5)(i): Adding 5 years to the original expiration date of the patent (i.e. **September 22, 2021**) or any earlier date set by terminal disclaimer	**September 22, 2026**
37 C.F.R. § 1.775(d)(5)(ii): Comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) with each other and selecting the earlier date	**September 11, 2023**

(14) Statement Acknowledging Duty to Disclose – § 1.740(a)(13)

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought in accordance with 37 C.F.R. § 1.765.

In compliance with this duty of disclosure, Applicant hereby discloses that two additional patent term extension applications are being filed for the approved product on even date herewith. The other patent term extension applications are being filed for:

(1) U.S. Patent No. 6,872,701 B2 (Attorney Docket No. P-088-US2); and

(2) U.S. Patent No. 7,208,471 B2 (Attorney Docket No. P-088-US5).

(15) Prescribed Fee – § 1.740(a)(14)

The Director is hereby authorized to charge the prescribed fees for receiving and acting upon this application ($1,120.00) to Deposit Account No. 50-0344, in the name of Theravance, Inc. The Director is also authorized to charge any additional fees required by this application, or to credit any overpayments, to Deposit Account No. 50-0344.

(16) Contact Person for Application – § 1.740(a)(15)

All inquires and correspondence relating to this application for patent term extension should be directed to:

Jeffrey A. Hagenah
Patent Department
Theravance, Inc.
901 Gateway Blvd.
South San Francisco, CA 94080
(650) 808-6406
(650) 808-6078 (fax)

(17) Submitted in Triplicate – § 1.740(b)

This application for extension of patent term including its attachments and supporting papers is being submitted as one original and two (2) additional copies (for a total of three copies).

III. CONCLUSION

Applicant respectfully requests consideration of this application for patent term extension and extension of the term of U.S. Patent No. 6,635,618 B2 for the full period permitted under 35 U.S.C. § 156.

Respectfully submitted,

THERAVANCE, INC.

Date: Oct. 13, 2009

By: _____
Jeffrey A. Hagenah, Ph.D.
Reg. No. 35,175
(650) 808-6406

THERAVANCE, INC.
901 Gateway Blvd.
South San Francisco, CA 94080
(650) 808-6000
(650) 808-6078 (Fax)

APPENDIX A

Copy of NDA 22-110 Approval Letter

Patent Term Extension Application

for

U.S. Patent No. 6,635,618 B2

(Attorney Docket No. P-088-US1)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-110

NDA APPROVAL

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated December 6, 2006, received December 19, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIBATIV (telavancin) for injection, 250 mg and 750 mg.

We also acknowledge receipt of your submissions dated March 13 (2), 20 and 25, May 5 (2), 13 and 29, June 1, 10 and 12, July 6, 13, 15, 17, 27, 28, 29 (2) and 30, and August 6, 12, 17, 18, 25 (2), 27 (2) and 28, and September 2 and 4, 2009.

The March 13, 2009, submission constituted a complete response to our action letter dated February 20, 2009.

This new drug application provides for the use of VIBATIV (telavancin) for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for ages 0 to 17 years for this application until December 31, 2014, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This study is listed below.

1529-001: Deferred pediatric study under PREA for the treatment of cSSSI in pediatric patients ages 0 to 17 years.

Final Report Submission: December 31, 2014

Submit final reports to this NDA. Use the following designator to prominently label all submissions:

"Required Pediatric Assessment(s)"

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on September 4, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. A survey of healthcare providers and patients' understanding of the serious risks of VIBATIV (telavancin)

b. A summary and analysis of maternal and fetal outcomes for all reported pregnancies (from any data source) including:
    1. A cumulative number of all fetal exposures and outcomes reported for all reported pregnancies
    2. A root cause analysis to investigate the pregnancies reported with VIBATIV (telavancin) use in the U.S.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 022110 REMS ASSESSMENT**

- **NEW SUPPLEMENT FOR NDA 022110**
  PROPOSED REMS MODIFICATION
  REMS ASSESSMENT

- **NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022110**
  REMS ASSESSMENT
  PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING REQUIREMENT UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of serious risks of teratogenicity or bacterial resistance.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1529-002: A pregnancy registry must be established to evaluate the safety of this product in pregnant women and their offspring. You will be required to evaluate the safety of VIBATIV (telavancin) use during pregnancy by developing and maintaining a prospective, observational pregnancy exposure registry study conducted in the United States. The study should compare pregnancy and fetal/infant outcomes of women exposed to VIBATIV (telavancin) during pregnancy to an unexposed control population. The registry should identify and record major congenital anomalies, minor anomalies that occur in groups of three or more, spontaneous

abortions, stillbirths, elective terminations, functional deficits in the child, and any serious pregnancy outcomes. Infants should be assessed through at least the first year of life. For more information, please refer to the FDA Guidance for Industry on Establishing Pregnancy Exposure Registries (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf). Your proposed Pregnancy Registry protocol submitted August 12, 2009, should be implemented prior to product launch.

The timetable you submitted on August 28, 2009, states that you will conduct this study according to the following timetable:

Final protocol Submission:	by 8/2009 (completed)
Interim Report:	by 9/2010, then annually
Study completion date:	by 6/2019
Final Report Submission:	by 12/2019

1529-003: Conduct a prospective study over a five-year period after introduction of VIBATIV (telavancin) to the market to determine if decreased susceptibility to VIBATIV (telavancin) is occurring in the target population of bacteria that are in the approved VIBATIV (telavancin) package insert. Provide a detailed study protocol describing the study to the Agency for review and comment before commencing the study.

The timetable you submitted on August 28, 2009, states that you will conduct this study according to the following timetable:

Final protocol Submission:	by 1/2010
Interim Report Submission:	by 3/2011, then annually
Study Completion Date:	by 12/2014
Final Report Submission:	by 5/2015

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENT

We remind you of your postmarketing commitment in your submission dated August 28, 2009:

1529-004: In order to determine if there may be some effect of renal function on the biological activity of VIBATIV (telavancin) that may explain the decreased efficacy of telavancin in patients with renal impairment, you have agreed to conduct the following:

a. Compare results obtained with the current analytical assay for determining concentrations of telavancin in plasma to results obtained with a bioassay method for patients with normal renal function, severe renal impairment (creatinine clearance <30 mL/min), and end-stage renal disease receiving hemodialysis.
b. The bioassay is to be reproducible with appropriate controls developed to determine if the test is performing correctly at the time subject specimens are tested.
c. Subjects are to be dosed per the Phase 3 cSSSI clinical trial protocols.
d. Enroll sufficient subjects with normal renal function, severe renal impairment, and end-stage renal disease receiving hemodialysis in the trial to obtain data from 15 evaluable patients for each subject population.

Final protocol Submission:	by 1/2010
Trial Completion Date:	by 2/2011
Final Report Submission:	by 6/2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each trial. Prominently identify all submissions, including supplements, with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKETING COMMITMENT FINAL REPORT**
- **POSTMARKETING COMMITMENT CORRESPONDENCE**

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling submitted September 2, 2009, and Medication Guide submitted August 18, 2009. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-110**."

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on July 13, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-110**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form.
For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Office Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: FDA Approved Labeling Text
Medication Guide
REMS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIBATIV safely and effectively. See full prescribing information for VIBATIV.

VIBATIV (telavancin) for injection, for intravenous use
Initial U.S. Approval: 2009

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING: FETAL RISK
See full prescribing information for complete boxed warning.

- **Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (8.1)**
- **Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. (8.1)**
- **Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. (8.1)**

----------INDICATIONS AND USAGE----------

VIBATIV is a lipoglycopeptide antibacterial indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- 10 mg/kg administered over 60 minutes by intravenous infusion once every 24 hours for 7 to 14 days. (2.1)
- Dosage adjustment in patients with renal impairment. (2.2):

Creatinine Clearance# (mL/min)	VIBATIV Dosage Regimen
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
10- ≤30	10 mg/kg every 48 hours

As calculated using the Cockcroft-Gault formula (12.3)

----------DOSAGE FORMS AND STRENGTHS ----------

Single-use vials containing either 250 or 750 mg telavancin. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients. (5.3)
- Decreased efficacy with moderate/severe baseline renal impairment: Consider these data when selecting antibacterial therapy for patients with baseline CrCl ≤50 mL/min. (5.4)
- Infusion-related reactions: Administer VIBATIV over at least 60 minutes to minimize infusion-related reactions. (5.5)
- *Clostridium difficile*-associated disease: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.6)
- QTc prolongation: Avoid use in patients at risk. Use with caution in patients taking drugs known to prolong the QT interval. (5.8)
- Coagulation test interference: Telavancin interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time. (5.9, 7.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥10% of patients treated with VIBATIV) include: taste disturbance, nausea, vomiting, and foamy urine. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)
- Pediatric patients: Safety and efficacy not demonstrated. (8.4)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised: 09/2009

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

WARNING: FETAL RISK

- **Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV**
- **Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus**
- **Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]***

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Complicated Skin and Skin Structure Infections

VIBATIV is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus)*, or *Enterococcus faecalis* (vancomycin-susceptible isolates only).

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV may be initiated as empiric therapy before results of these tests are known.

2 DOSAGE AND ADMINISTRATION

2.1 Complicated Skin and Skin Structure Infections

The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period in patients ≥18 years of age by intravenous infusion once every 24 hours for 7 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

2.2 Patients with Renal Impairment

Because telavancin is eliminated primarily by the kidney, a dosage adjustment is required for patients whose creatinine clearance is ≤50 mL/min, as listed in Table 1 *[see Clinical Pharmacology (12.3)]*.

Table 1: Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	VIBATIV Dosage Regimen
>50	10 mg/kg every 24 hours
30 - 50	7.5 mg/kg every 24 hours
10 - ≤30	10 mg/kg every 48 hours

* As calculated using the Cockcroft-Gault formula [see *Clinical Pharmacology (12.3)*]

There is insufficient information to make specific dosage adjustment recommendations for patients with end-stage renal disease (CrCl <10 mL/min), including patients undergoing hemodialysis.

2.3 Preparation and Administration

250 mg vial: Reconstitute the contents of a VIBATIV 250 mg vial with **15** mL of 5% Dextrose Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP. The resultant solution has a concentration of 15 mg/mL (total volume of approximately 17.0 mL).

750 mg vial: Reconstitute the contents of a VIBATIV 750 mg vial with **45** mL of 5% Dextrose Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP, The resultant solution has a concentration of 15 mg/mL (total volume of approximately 50.0 mL).

The following formula can be used to calculate the volume of reconstituted VIBATIV solution required to prepare a dose:

Telavancin dose (mg) = 10 mg/kg or 7.5 mg/kg x patient weight (in kg) (see Table 1)

$$\textbf{Volume of reconstituted solution (mL)} = \frac{\textbf{Telavancin dose (mg)}}{\textbf{15 mg/mL}}$$

For doses of 150 to 800 mg, the appropriate volume of reconstituted solution must be further diluted in 100 to 250 mL prior to infusion. Doses less than 150 mg or greater than 800 mg should be further diluted in a volume resulting in a final concentration of 0.6 to 8 mg/mL. Appropriate infusion solutions include: 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The dosing solution should be administered by intravenous infusion over a period of 60 minutes.

Reconstitution time is generally under 2 minutes, but can sometimes take up to 20 minutes. Mix thoroughly to reconstitute and check to see if the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration. Discard the vial if the vacuum did not pull the diluent into the vial.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparing the final intravenous solution. Studies have shown that the reconstituted solution in the vial should be used within 4 hours when stored at room temperature or within 72 hours under refrigeration at 2 to 8°C (36 to 46°F). The diluted (dosing) solution in the infusion bag should be used within 4 hours when stored at room temperature or used within 72 hours when stored under refrigeration at 2 to 8°C (36 to 46°F). However, the total time in the vial plus the time in the infusion bag should not exceed 4 hours at room temperature and 72 hours under refrigeration at 2 to 8°C (36 to 46°F).

VIBATIV is administered intravenously. Because only limited data are available on the compatibility of VIBATIV with other IV substances, additives or other medications should not be added to VIBATIV single-use vials or infused simultaneously through the same IV line. If the same intravenous line is used for sequential infusion of additional medications, the line should be flushed before and after infusion of VIBATIV with 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

VIBATIV is supplied in single-use vials containing either 250 or 750 mg telavancin as a sterile, lyophilized powder.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Women of Childbearing Potential

Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

5.2 Pregnancy

Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in 3 animal species at clinically relevant doses. This raises concern about potential adverse developmental outcomes in humans *[see Use in Specific Populations (8.1)]*.

5.3 Nephrotoxicity

Increases in serum creatinine to 1.5 times baseline occurred more frequently among VIBATIV-treated patients with normal baseline serum creatinine (15%) compared with vancomycin-treated patients with normal baseline serum creatinine (7%).

In 30/929 (3.1%) of VIBATIV-treated patients compared to 10/938 (1.1%) of vancomycin-treated patients, renal adverse events indicative of renal impairment occurred, as defined by the following terms: increased serum creatinine, renal impairment, renal insufficiency, and/or renal failure. In 17 of the 30 VIBATIV-treated patients, these adverse events had not completely resolved by the end of the trials, compared with 6 of the 10 vancomycin-treated patients. Serious adverse events indicative of renal impairment occurred in 11/929 (1.2%) of VIBATIV-treated patients compared to 3/938 (0.3%) of vancomycin-treated patients. Twelve patients treated with VIBATIV discontinued treatment due to adverse events indicative of renal impairment compared to 2 patients treated with vancomycin. Adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension). The renal adverse event rate was also higher in patients who received concomitant medications known to affect kidney function (eg, non-steroidal anti-inflammatory drugs, ACE inhibitors, and loop diuretics). Fifteen of 174 patients (8.6%)

≥65 years of age had adverse events indicative of renal impairment compared to 16 of 755 patients (1.9%) <65 years of age *[see Use in Specific Populations (8.5)]*.

Monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (at 48- to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed *[see Dosage and Administration, Clinical Pharmacology (2.2)]*.

In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-cyclodextrin can occur *[see Patients with Renal Impairment (8.6) and Clinical Pharmacology (12.3)]*.

5.4 Decreased Efficacy with Moderate/Severe Baseline Renal Impairment

In a subgroup analysis of the pooled cSSSI studies, clinical cure rates in the telavancin-treated patients were lower in patients with baseline CrCl ≤50 mL/min compared to those with CrCl >50 mL/min (Table 2). A decrease of this magnitude was not observed in vancomycin-treated patients. Consider these data when selecting antibacterial therapy for use in patients with baseline moderate/severe renal impairment.

Table 2: Clinical Cure by Baseline Renal Function

	VIBATIV % (n/N)	**Vancomycin % (n/N)**
ATe Population[1]		
CrCl >50 mL/min	75.3% (565/750)	73.7% (575/780)
CrCl ≤50 mL/min	63.1% (70/111)	69.4% (75/108)
CE Population[2]		
CrCl >50 mL/min	87.0% (520/598)	85.9% (524/610)
CrCl ≤50 mL/min	67.4% (58/86)	82.7% (67/81)

[1] All-treated population - includes all patients randomized, treated, and evaluated for efficacy
[2] Clinically evaluable population

5.5 Infusion-Related Reactions

VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause "Red-man Syndrome"-like

reactions including: flushing of the upper body, urticaria, pruritus, or rash. Stopping or slowing the infusion may result in cessation of these reactions.

5.6 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hyper-toxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.7 Development of Drug-Resistant Bacteria

Prescribing VIBATIV in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibacterial drugs, use of VIBATIV may result in overgrowth of nonsusceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

5.8 QTc Prolongation

In a study involving healthy volunteers, doses of 7.5 and 15 mg/kg of VIBATIV prolonged the QTc interval *[see Clinical Pharmacology (12.2)]*. Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. Patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy were not included in clinical trials of VIBATIV. Use of VIBATIV should be avoided in patients with these conditions.

5.9 Coagulation Test Interference

Although telavancin does not interfere with coagulation, it interfered with certain tests used to monitor coagulation (Table 3), when conducted using samples drawn 0 to 18 hours after VIBATIV administration for patients being treated once every 24 hours. Blood samples for these coagulation tests should be collected as close as possible prior to a patient's next dose of VIBATIV. Blood samples for coagulation tests unaffected by VIBATIV may be collected at any time *[see Drug Interactions (7.1)]*.

Table 3: Coagulation Tests Affected and Unaffected by Telavancin

Affected by Telavancin	Unaffected by Telavancin
Prothrombin time	Thrombin time
International normalized ratio	Whole blood (Lee-White) clotting time
Activated partial thromboplastin time	Ex vivo platelet aggregation
Activated clotting time	Chromogenic factor Xa assay
Coagulation based factor Xa tests	Functional (chromogenic) factor X assay
	Bleeding time
	D-dimer
	Fibrin degradation products

No evidence of increased bleeding risk has been observed in clinical trials with VIBATIV. Telavancin has no effect on platelet aggregation. Furthermore, no evidence of hypercoagulability has been seen, as healthy subjects receiving VIBATIV have normal levels of D-dimer and fibrin degradation products.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Nephrotoxicity *[see Warnings and Precautions (5.3)]*
- Infusion-related reactions *[see Warnings and Precautions (5.5)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.6)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The two Phase 3 cSSSI clinical trials (Trial 1 and Trial 2) for VIBATIV included 929 adult patients treated with VIBATIV at 10 mg/kg IV once daily. The mean age of patients treated with VIBATIV was 49 years (range 18-96). There was a slight male predominance (56%) in patients treated with VIBATIV, and patients were predominantly Caucasian (78%).

In the cSSSI clinical trials, <1% (8/929) patients who received VIBATIV died and <1% (8/938) patients treated with vancomycin died. Serious adverse events were reported in 7% (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated patients, and most commonly included cardiac, respiratory, or infectious events. Treatment discontinuations due to adverse events occurred in 8% (72/929) of patients treated with VIBATIV, the most common events being nausea and rash (~1% each). Treatment discontinuations due to adverse events occurred in 6% (53/938) of vancomycin-treated patients, the most common events being rash and pruritus (~1% each).

The most common adverse reactions occurring in ≥10% of VIBATIV-treated patients observed in the VIBATIV Phase 3 cSSSI trials were taste disturbance, nausea, vomiting, and foamy urine.

Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in >2% of patients treated with VIBATIV possibly related to the drug (including those reactions known to occur with other glycopeptide antibacterial agents).

Table 4: Incidence of Treatment-emergent Adverse Drug Reactions Reported in ≥2% of VIBATIV or Vancomycin Patients Treated in Trial 1 and Trial 2

	VIBATIV (N=929)	**Vancomycin (N=938)**
Body as a Whole		
Rigors	4%	2%
Generalized pruritus	3%	6%
Digestive System		
Nausea	27%	15%
Vomiting	14%	7%
Diarrhea	7%	8%
Abdominal pain	2%	2%

	VIBATIV (N=929)	Vancomycin (N=938)
Metabolic and Nutritional		
Decreased appetite	3%	2%
Nervous System		
Taste disturbance[1]	33%	7%
Dizziness	6%	6%
Renal System		
Foamy urine	13%	3%
Skin and Appendages		
Pruritus	6%	13%
Rash	4%	5%
Other		
Infusion site pain	4%	4%
Infusion site erythema	3%	3%

[1] Described as a metallic or soapy taste.

7 DRUG INTERACTIONS

7.1 Drug-Laboratory Test Interactions

Effects of Telavancin on Coagulation Test Parameters

Telavancin binds to the artificial phospholipid surfaces added to common anticoagulation tests, thereby interfering with the ability of the coagulation complexes to assemble on the surface of the phospholipids and promote clotting in vitro. These effects appear to depend on the type of reagents used in commercially available assays. Thus, when measured shortly after completion of an infusion of VIBATIV, increases in the PT, INR, aPTT, and ACT have been observed. These effects dissipate over time, as plasma concentrations of telavancin decrease.

Urine Protein Tests

Telavancin interferes with urine qualitative dipstick protein assays, as well as quantitative dye methods (e.g., pyrogallol red-molybdate). However, microalbumin assays are not affected and can be used to monitor urinary protein excretion during VIBATIV treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the VIBATIV pregnancy registry by calling 1-888-658-4228.

Fetal Risk Summary

All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about 15%), or other adverse outcomes regardless of drug exposure.

There are no data on VIBATIV use in pregnant women. In 3 animal species, VIBATIV exposure during pregnancy at clinically relevant doses caused reduced fetal weights and increased rates of digit and limb malformations in offspring. These data raise concern about potential adverse developmental outcomes in humans (see *Data*).

Clinical Considerations

Given the lack of human data and the risks suggested by animal data, avoid using VIBATIV in pregnant women unless the benefits to the patient outweigh the potential risks to the fetus.

Data

Human Data

There are no data on human pregnancies exposed to VIBATIV.

Animal Data

In embryo-fetal development studies in rats, rabbits, and minipigs, telavancin demonstrated the potential to cause limb and skeletal malformations when given intravenously during the period of organogenesis at doses up to 150, 45 or 75 mg/kg/day, respectively. These doses resulted in exposure levels approximately 1- to 2-fold the human exposure (AUC) at the maximum clinical recommended dose. Malformations observed at <1% (but absent or at lower rates in historical or concurrent controls), included brachymelia (rats and rabbits), syndactyly (rats, minipigs), adactyly (rabbits), and polydactyly (minipigs). Additional findings

in rabbits included flexed front paw and absent ulna, and in the minipigs included misshapen digits and deformed front leg. Fetal body weights were decreased in rats.

In a prenatal/perinatal development study, pregnant rats received intravenous telavancin at up to 150 mg/kg/day (approximately the same AUC as observed at the maximum clinical dose) from the start of organogenesis through lactation. Offspring showed decreases in fetal body weight and an increase in the number of stillborn pups. Brachymelia was also observed. Developmental milestones and fertility of the pups were unaffected.

8.3 Nursing Mothers

It is not known whether telavancin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIBATIV is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of VIBATIV in pediatric patients has not been studied.

8.5 Geriatric Use

Of the 929 patients treated with VIBATIV at a dose of 10 mg/kg once daily in clinical trials of cSSSI, 174 (18.7%) were ≥65 years of age and 87 (9.4%) were ≥75 years of age. In the cSSSI trials, lower clinical cure rates were observed in patients ≥65 years of age compared with those <65 years of age. Overall, treatment-emergent adverse events occurred with similar frequencies in patients ≥65 (75% of patients) and <65 years of age (83% of patients). Fifteen of 174 (8.6%) patients ≥65 years of age treated with telavancin had adverse events indicative of renal impairment compared to 16 of 755 (1.9%) patients <65 years of age *[see Warnings and Precautions (5.3), Clinical Trials (14.1)]*.

Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

The mean plasma AUC values of telavancin were similar in healthy young and elderly subjects. Dosage adjustment for elderly patients should be based on renal function *[see Dosage and Administration, Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

The cSSSI trials included patients with normal renal function and patients with varying degrees of renal impairment. Patients with underlying renal dysfunction or risk factors for renal dysfunction had a higher incidence of renal adverse events *[see Warnings and Precautions (5.3)]*. Patients with creatinine clearance ≤50 mL/min also had lower clinical cure rates. Consider these data when selecting antibacterial therapy in patients with baseline moderate/ severe renal impairment (CrCl ≤50 mL/min).

Dosage adjustment is required in patients with ≤50 mL/min renal impairment *[see Dosage and Administration (2.2)]*. There is insufficient information to make specific dosage adjustment recommendations for patients with end-stage renal disease (CrCl <10 mL/min), including patients receiving hemodialysis *[see Overdosage (10), Clinical Pharmacology (12.3)]*.

Hydroxypropyl-beta-cyclodextrin is excreted in urine and may accumulate in patients with renal impairment. Serum creatinine should be closely monitored and, if renal toxicity is suspected, an alternative agent should be considered [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*].

8.7 Patients with Hepatic Impairment

The cSSSI trials included patients with normal hepatic function and with hepatic impairment. No dosage adjustment is recommended in patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdosage, VIBATIV should be discontinued and supportive care is advised with maintenance of glomerular filtration and careful monitoring of renal function. Following administration of a single dose of VIBATIV 7.5 mg/kg to subjects with end-stage renal disease, approximately 5.9% of the administered dose of telavancin was recovered in the dialysate following 4 hours of hemodialysis. However, no information is available on the use of hemodialysis to treat an overdosage *[see Clinical Pharmacology (12.3)]*.

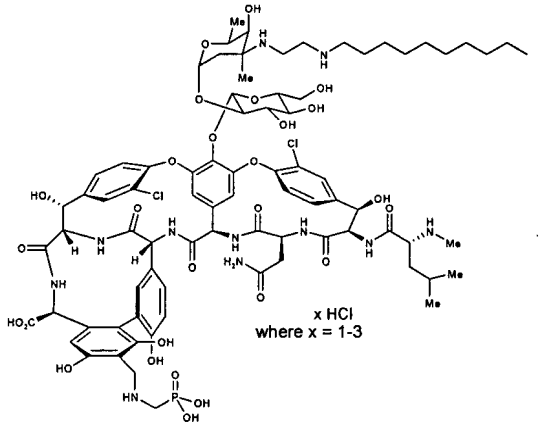
The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was evaluated in an in vitro study *[see Nonclinical Toxicology (13.2)]*. Telavancin was cleared by CVVH and the clearance of telavancin increased with increasing ultrafiltration rate. However, the clearance of telavancin by CVVH has not been evaluated in a clinical study;

thus, the clinical significance of this finding and use of CVVH to treat an overdosage is unknown.

11 DESCRIPTION

VIBATIV contains telavancin hydrochloride, a lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. The chemical name of telavancin hydrochloride is vancomycin,N3"-[2-(decylamino)ethyl]-29-[[(phosphono-methyl)-amino]-methyl]-hydrochloride. Telavancin hydrochloride has the following chemical structure:

Figure 1: Telavancin Hydrochloride



Telavancin hydrochloride

Telavancin hydrochloride is an off-white to slightly colored amorphous powder with the empirical formula $C_{80}H_{106}C_{12}N_{11}O_{27}P \cdot xHCl$ (where x = 1 to 3) and a free-base molecular weight of 1755.6. It is highly lipophilic and slightly soluble in water.

VIBATIV is a sterile, preservative-free, white to slightly colored lyophilized powder containing telavancin hydrochloride (equivalent to either 250 mg or 750 mg of telavancin as the free base) for intravenous use. The inactive ingredients are Hydroxypropylbetadex, Ph. Eur (hydroxypropyl-beta-cyclodextrin) (2500 mg per 250 mg telavancin, 7500 mg per 750 mg telavancin), mannitol (312.5 mg per 250 mg telavancin, 937.5 mg per 750 mg telavancin), and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment. When reconstituted, it forms a clear to slightly colored solution with a pH of 4.5 (4.0 to 5.0).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Telavancin is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

The antimicrobial activity of telavancin appears to best correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC) for *Staphylococcus aureus* based on animal models of infection. An exposure-response analysis of 2 cSSSI clinical trials supports the dose of 10 mg/kg every 24 hours.

Cardiac Electrophysiology

The effect of telavancin on cardiac repolarization was assessed in a randomized, double-blind, multiple-dose, positive-controlled, and placebo-controlled, parallel study (n=160). Healthy subjects received VIBATIV 7.5 mg/kg, VIBATIV 15 mg/kg, positive control, or placebo infused over 60 minutes once daily for 3 days. Based on interpolation of the data from VIBATIV 7.5 mg/kg and 15 mg/kg, the mean maximum baseline-corrected, placebo-corrected QTc prolongation at the end of infusion was estimated to be 12-15 msec for VIBATIV 10 mg/kg and 22 msec for the positive control (Table 5). By 1 hour after infusion the maximum QTc prolongation was 6-9 msec for VIBATIV and 15 msec for the positive control.

Table 5: Mean and Maximum QTcF Changes from Baseline Relative to Placebo

	QTcF[1] Change from Baseline	
	Mean (Upper 90% Confidence Limit[2]) msec	**Maximum (Upper 90% Confidence Limit) msec**
VIBATIV 7.5 mg/kg	4.1 (7)	11.6 (16)
VIBATIV 15 mg/kg	4.6 (8)	15.1 (20)
Positive Control	9.5 (13)	21.6 (26)

[1] Fridericia corrected

[2] Upper CL from a 2-sided 90% CI on difference from placebo (msec)

ECGs were performed prior to and during the treatment period in patients receiving VIBATIV 10 mg/kg in 3 studies to monitor QTc intervals. In these trials, 214 of 1029 (21%) patients allocated to treatment with VIBATIV and 164 of 1033 (16%) allocated to vancomycin

received concomitant medications known to prolong the QTc interval and are known to be associated with definite or possible risk of torsades de pointes. The incidence of QTc prolongation >60 msec was 1.5% (15 patients) in the VIBATIV group and 0.6% (6 patients) in the vancomycin group. Nine of the 15 VIBATIV patients received concomitant medications known to prolong the QTc interval and definitely or possibly associated with a risk of torsades de pointes, compared with 1 of the 6 patients who received vancomycin. A similar number of patients in each treatment group (<1%) who did not receive a concomitant medication known to prolong the QTc interval experienced a prolongation >60 msec from baseline. In a separate analysis, 1 patient in the VIBATIV group and 2 patients in the vancomycin group experienced QTc >500 msec. No cardiac adverse events were ascribed to prolongation of the QTc interval.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of telavancin (10mg/kg) after a single and multiple 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in Table 6.

Table 6: Pharmacokinetic Parameters of Telavancin in Healthy Adults, 10 mg/kg

	Single Dose	**Multiple Dose**
	(n=42)	**(n=36)**
C_{max} (mcg/mL)	93.6 ± 14.2	108 ± 26
$AUC_{0-\infty}$ (mcg·hr/mL)	747 ± 129	--[1]
AUC_{0-24h} (mcg·hr/mL)	666 ± 107	780 ± 125
$t_{1/2}$ (hr)	8.0 ± 1.5	8.1 ± 1.5
Cl (mL/hr/kg)	13.9 ± 2.9	13.1 ± 2.0
V_{ss} (mL/kg)	145 ± 23	133 ± 24

C_{max} maximum plasma concentration
AUC area under concentration-time course
$t_{1/2}$ terminal elimination half-life
Cl clearance
V_{ss} apparent volume of distribution at steady state
[1] Data not available

In healthy young adults, the pharmacokinetics of telavancin administered intravenously were linear following single doses from 5 to 12.5 mg/kg and multiple doses from 7.5 to 15 mg/kg administered once-daily for up to 7 days. Steady-state concentrations were achieved by the third daily dose.

Distribution

Telavancin binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean binding is approximately 90% and is not affected by renal or hepatic impairment.

Concentrations of telavancin in skin blister fluid were 40% of those in plasma ($AUC_{0\text{-}24hr}$ ratio) after 3 daily doses of 7.5 mg/kg VIBATIV in healthy young adults.

Metabolism

No metabolites of telavancin were detected in in vitro studies using human liver microsomes, liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered by inhibitors of any of these enzymes.

In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated metabolites were identified with the predominant metabolite (THRX-651540) accounting for <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic pathway for telavancin has not been identified.

Excretion

Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately 76% of the administered dose was recovered from urine and <1% of the dose was recovered from feces (collected up to 216 hours) based on total radioactivity.

Specific Populations

Geriatric Patients

The impact of age on the pharmacokinetics of telavancin was evaluated in healthy young (range 21-42 years) and elderly (range 65-83 years) subjects. The mean CrCl of elderly subjects was 66 mL/min. Age alone did not have a clinically meaningful impact on the pharmacokinetics of telavancin *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

The pharmacokinetics of telavancin in patients less than 18 years of age have not been studied.

Gender

The impact of gender on the pharmacokinetics of telavancin was evaluated in healthy male (n=8) and female (n=8) subjects. The pharmacokinetics of telavancin were similar in males and females. No dosage adjustment is recommended based on gender.

Renal Impairment

The pharmacokinetics of telavancin were evaluated in subjects with normal and subjects with varying degrees of renal impairment following administration of a single dose of telavancin 7.5 mg/kg (n=28). The mean $AUC_{0-\infty}$ values were approximately 13%, 29%, and 118% higher for subjects with CrCl >50 to 80 mL/min, CrCl 30 to 50 mL/min, and CrCl ≤30 mL/min, respectively, compared to subjects with normal renal function. Dosage adjustment is required in patients with CrCl ≤50 mL/min *[see Dosage and Administration (2.2)]*.

Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^*}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

*Use actual body weight if < ideal body weight (IBW)
IBW (male) = 50 kg + 0.9 kg/cm over 152 cm height
IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

Following administration of a single dose of VIBATIV 7.5 mg/kg to subjects with end-stage renal disease, approximately 5.9% of the administered dose of telavancin was recovered in the dialysate following 4 hours of hemodialysis. The effects of peritoneal dialysis have not been studied.

Following a single intravenous dose of VIBATIV 7.5 mg/kg, the clearance of hydroxypropyl-beta-cyclodextrin was reduced in subjects with renal impairment, resulting in a higher exposure to hydroxypropyl-beta-cyclodextrin. In subjects with mild, moderate, and severe

renal impairment, the mean clearance values were 38%, 59%, and 82% lower, respectively, compared to subjects with normal renal function. Multiple infusions of VIBATIV may result in accumulation of hydroxypropyl-beta-cyclodextrin.

Hepatic Impairment

The pharmacokinetics of telavancin were not altered in subjects with moderate hepatic impairment (n= 8, Child-Pugh B) compared to healthy subjects with normal hepatic function matched for gender, age, and weight. The pharmacokinetics of telavancin have not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

Drug Interactions

In Vitro

The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP 3A4/5 at potentially clinically relevant concentrations. Upon further evaluation in a Phase 1 clinical trial, telavancin was found not to inhibit the metabolism of midazolam, a sensitive CYP3A substrate (see below).

Midazolam

The impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was evaluated in 16 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg, intravenous midazolam 1 mg, and both. The results showed that telavancin had no impact on the pharmacokinetics of midazolam and midazolam had no effect on the pharmacokinetics of telavancin. Therefore, telavancin is unlikely to alter the pharmacokinetics of drugs metabolized by the CYP450 system to a clinically significant degree.

Aztreonam

The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg, aztreonam 2 gm, and both. Telavancin had no impact on the pharmacokinetics of aztreonam and aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of telavancin or aztreonam is recommended when both drugs are coadministered.

Piperacillin-tazobactam

The impact of telavancin on the pharmacokinetics of piperacillin-tazobactam was evaluated in 12 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg, piperacillin-tazobactam 4.5 g, and both. Telavancin had no impact on the pharmacokinetics of piperacillin-tazobactam and piperacillin-tazobactam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of telavancin or piperacillin-tazobactam is recommended when both drugs are coadministered.

12.4 Microbiology

Telavancin is a semisynthetic, lipoglycopeptide antibiotic. Telavancin exerts concentration-dependent, bactericidal activity against Gram-positive organisms in vitro, as demonstrated by time-kill assays and MBC/MIC (minimum bactericidal concentration/minimum inhibitory concentration) ratios using broth dilution methodology. In vitro studies demonstrated a telavancin post-antibiotic effect ranging from 1 to 6 hours against *S. aureus* and other Gram-positive pathogens.

Although telavancin is approximately 90% protein bound, the presence of human serum or human serum albumin has minimal impact on the in vitro activity of telavancin against staphylococci, streptococci, and vancomycin-susceptible enterococci.

Mechanism of Action

Telavancin inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan. Telavancin binds to the bacterial membrane and disrupts membrane barrier function.

Interactions with Other Antibacterials

In vitro investigations demonstrated no antagonism between telavancin and amikacin, aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem, oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole, when tested in various combinations against telavancin susceptible staphylococci, streptococci, and enterococci. This information is not available for other bacteria.

Cross-Resistance

Some vancomycin-resistant enterococci have a reduced susceptibility to telavancin. There is no known cross-resistance between telavancin and other classes of antibiotics.

Antibacterial Activity

Telavancin has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections as described in the Indications and Usage section *[see Indications and Usage (1.1)]*:

Facultative Gram-Positive Microorganisms

Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus pyogenes
Enterococcus faecalis (vancomycin-susceptible isolates only)
Streptococcus agalactiae
Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)

Greater than 90% of the following microorganisms exhibit an in vitro MIC less than or equal to the telavancin-susceptible breakpoint for organisms of similar genus shown in Table 7. The safety and effectiveness of telavancin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Facultative Gram-Positive Microorganisms

Enterococcus faecium (vancomycin-susceptible isolates only)
Staphylococcus haemolyticus
Streptococcus dysgalactaie subsp. *equisimilis*
Staphylococcus epidermidis

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution technique

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure *[see References (15)]*. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of telavancin powder. The MIC values should be interpreted according to the criteria provided in Table 7.

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations *[see References (15)]*. This procedure uses paper disks impregnated with 30 mcg of telavancin to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive criteria are provided in Table 7.

Table 7: Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria[1]					
	Minimal inhibitory concentration (mcg/mL)			**Disk Diffusion zone diameter (mm)**		
	S	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 1	--	--	≥ 15	--	--
Streptococcus pyogenes *Streptococcus agalactiae* *Streptococcus anginosus group*	≤ 0.12	--	--	≥ 15	--	--
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤ 1	--	--	≥ 15	--	--

1 The current absence of resistant isolates precludes defining any results other than "susceptible" Isolates yielding results other than susceptible should be subjected to additional testing

A report of "susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard telavancin powder should provide the range of values noted in Table 8.

Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 8: Acceptable Quality Control Ranges for Telavancin to be used in Validation of Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimal Inhibitory Concentration (mcg/mL)	**Disk Diffusion Zone Diameter (mm)**
Enterococcus faecalis ATCC 29212	0.12-0.5	Not applicable
Staphylococcus aureus ATCC 29213	0.12-1	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	16-20
Streptococcus pneumoniae ATCC 49619[1]	0.004-0.03	17-24

[1] This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to determine the carcinogenic potential of telavancin have not been performed.

Neither mutagenic nor clastogenic potential of telavancin was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion), an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay.

Telavancin did not affect the fertility or reproductive performance of adult male rats (exposed to telavancin for at least 4 weeks prior to mating) or female rats (exposed to telavancin for at least 2 weeks prior to mating).

Male rats given telavancin for 6 weeks, at exposures similar to those measured in clinical studies, displayed altered sperm parameters that were reversible following an 8-week recovery period.

13.2 Animal Toxicology and/or Pharmacology

Two-week administration of telavancin in rats produced minimal renal tubular vacuolization with no changes in BUN or creatinine. These effects were not seen in studies conducted in dogs for similar duration. Four weeks of treatment resulted in reversible elevations in BUN and/or creatinine in association with renal tubular degeneration that further progressed following 13 weeks of treatment.

These effects occurred at exposures (based on AUCs) that were similar to those measured in clinical trials.

The potential effects of continuous venovenous hemofiltration (CVVH) on the clearance of telavancin were examined in an in vitro model using bovine blood. Telavancin was cleared by CVVH and the clearance of telavancin increased with increasing ultrafiltration rate *[see Overdosage (10)]*.

14 CLINICAL TRIALS

14.1 Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections (cSSSI) were enrolled in two randomized, multinational, multicenter, double-blinded trials (Trial 1 and Trial 2) comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g IV every 12 hours) for 7 to 14 days. Vancomycin dosages could be adjusted per site-specific practice. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. These trials were identical in design, enrolling approximately 69% of their patients from the United States.

The trials enrolled adult patients with cSSSI with suspected or confirmed MRSA as the primary cause of infection. The all-treated efficacy (ATe) population included all patients who received any amount of study medication according to their randomized treatment group and were evaluated for efficacy. The clinically evaluable population (CE) included patients in the ATe population with sufficient adherence to the protocol.

The ATe population consisted of 1,794 patients. Of these, 1,410 (78.6%) patients were clinically evaluable (CE). Patients with demographic and baseline characteristics were well-balanced between treatment groups and are presented in Table 9.

Table 9: Baseline Infection Types in Patients in Trials 1 and 2 – ATe Population

	VIBATIV (N=884)[1]	Vancomycin (N=910)[1]
Type of infection		
Major Abscess	375 (42.4%)	397 (43.6%)
Deep/Extensive Cellulitis	309 (35.0%)	337 (37.0%)
Wound Infection	139 (15.7%)	121 (13.3%)
Infected Ulcer	45 (5.1%)	46 (5.1%)
Infected Burn	16 (1.8%)	9 (1.0%)

[1] Includes all patients randomized, treated, and evaluated for efficacy

The primary efficacy endpoints in both trials was the clinical cure rates at a follow-up (Test of Cure) visit in the ATe and CE populations. Clinical cure rates in Trials 1 and 2 are displayed for the ATe and CE population in Table 10.

Table 10: Clinical Cure at Test-of-Cure in Trials 1 and 2 - ATe and CE Populations

	Trial 1			Trial 2		
	VIBATIV	Vancomycin	Difference	VIBATIV	Vancomycin	Difference
	% (n/N)	% (n/N)	(95% CI)[1]	% (n/N)	% (n/N)	(95% CI)[1]
ATe	72.5% (309/426)	71.6% (307/429)	0.9 (-5.3, 7.2)	74.7% (342/458)	74.0% (356/481)	0.7 (-5.1, 6.5)
CE	84.3% (289/343)	82.8% (288/348)	1.5 (-4.3, 7.3)	83.9% (302/360)	87.7% (315/359)	-3.8 (-9.2, 1.5)

[1] 95% CI computed using a continuity correction

The cure rates by pathogen for the microbiologically evaluable (ME) population are presented in Table 11.

Table 11: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in Trials 1 and 2 – ME Population[1]

	VIBATIV % (n/N)	Vancomycin % (n/N)
Staphylococcus aureus (MRSA)	87.0% (208/239)	85.9% (225/262)

	VIBATIV % (n/N)	**Vancomycin % (n/N)**
Staphylococcus aureus (MSSA)	82.0% (132/161)	85.1% (131/154)
Enterococcus faecalis	95.6% (22/23)	80.0% (28/35)
Streptococcus pyogenes	84.2% (16/19)	90.5% (19/21)
Streptococcus agalactiae	73.7% (14/19)	86.7% (13/15)
Streptococcus anginosus group	76.5% (13/17)	100.0% (9/9)

[1] The ME population included patients in the CE population who had Gram positive pathogens isolated at baseline and had central identification and susceptibility of the microbiological isolate(s)

In the two cSSSI trials, clinical cure rates were similar across gender and race. Clinical cure rates in the telavancin clinically evaluable (CE) population were lower in patients ≥65 years of age compared to those <65 years of age. A decrease of this magnitude was not observed in the vancomycin CE population. Clinical cure rates in the telavancin CE population <65 years of age were 503/581 (86.6%) and in those ≥65 years were 88/122 (72.1%). In the vancomycin CE population clinical cure rates in patients <65 years of age were 492/570 (86.3%) and in those ≥65 years was 111/137 (82.0%). Clinical cure rates in the telavancin-treated patients were lower in patients with baseline CrCl ≤50 mL/min compared to those with CrCl >50 mL/min. A decrease of this magnitude was not observed in the vancomycin-treated patients *[see Warnings and Precautions (5.4)]*.

15 REFERENCES

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2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard – 10th ed. CLSI document M2-A10; CLSI, Wayne, PA. 19087-1898, 2009.

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16 HOW SUPPLIED/STORAGE AND HANDLING

- Cartons of 10 individually packaged 250 mg single-dose vials (NDC 0469-3525-30)
- Cartons of 10 individually packaged 750 mg single-dose vials (NDC 0469-3575-50)

Store original packages at refrigerated temperatures of 2 to 8°C (35 to 46 °F). Excursions to ambient temperatures (up to 25 °C (77 °F)) are acceptable. Avoid excessive heat.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

Use during Pregnancy and by Women of Childbearing Potential

Women of childbearing potential (those who have **not** had: complete absence of menses for at least 24 months or medically confirmed menopause, medically confirmed primary ovarian failure, a history of hysterectomy, bilateral oophorectomy, or tubal ligation) should:

- Be informed about the potential risk of fetal harm if VIBATIV is used during pregnancy
- Have a pregnancy test prior to administration of VIBATIV
- If not pregnant, use effective contraceptive methods to prevent pregnancy during VIBATIV treatment
- Notify their prescribing physician/ healthcare provider if they become pregnant during VIBATIV treatment

Pregnancy Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the pregnancy registry by calling 1-888-658-4228.

Diarrhea

Diarrhea is a common problem caused by antibiotics that usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having received the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Correct Use of Antibacterial Drugs

Patients should be counseled that antibacterial drugs including VIBATIV should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When VIBATIV is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of immediate treatment, and (2) increase the likelihood that the bacteria will develop resistance and will not be treatable by VIBATIV or other antibacterial drugs in the future.

Common Adverse Effects

Patients should be informed about the common adverse effects of VIBATIV including taste disturbance, nausea, vomiting, headache, and foamy urine. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom, or if any known symptom persists or worsens. Patients should be instructed to inform their healthcare provider of any other medications they are currently taking with VIBATIV, including over-the-counter medications.

Manufactured for:
Theravance, Inc.
South San Francisco, CA 94080

Marketed by:
Astellas Pharma US, Inc.
Deerfield, IL 60015

US Patent Nos. 6,635,618 B2; 6,858,584 B2; 6,872,701 B2; 7,008,923 B2; 7,208,471 B2; 7,351,691 B2; 7,531,623 B2; and 7,544,364 B2

VIBATIV is a trademark of Astellas Pharma Inc.

MEDICATION GUIDE

VIBATIV (vy-'ba-tiv)

(telavancin)

for injection

Read this Medication Guide before you start taking VIBATIV and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VIBATIV?

VIBATIV may harm your unborn baby. Women who can become pregnant should have a blood pregnancy test before taking VIBATIV.

- Talk to your healthcare provider if you are pregnant or plan to become pregnant. Your healthcare provider will decide if VIBATIV is the right medicine for you
- Do not become pregnant while taking VIBATIV. Women who can become pregnant should use effective birth control (contraception) while taking VIBATIV
- If you get pregnant while taking VIBATIV, tell your healthcare provider right away
- If you become pregnant while taking VIBATIV, talk to your healthcare provider about taking part in the VIBATIV Pregnancy Registry. This is a study to learn how VIBATIV affects pregnancy and babies. You can enroll in this registry by calling 1- 888-658-4228

What is VIBATIV?

VIBATIV is a prescription antibiotic medicine used in adults, alone or with other medicines to treat certain types of germs (bacteria) that cause serious skin infections.

It is not known if VIBATIV is safe or effective in children under 18 years of age.

What should I tell my healthcare provider before taking VIBATIV?

Before you take VIBATIV, tell your healthcare provider if you:

- have kidney problems
- have diabetes
- have heart problems, including QTC prolongation or a family history of it
- have high blood pressure
- have other medical conditions
- are breastfeeding or plan to breastfeed. It is not known if VIBATIV passes into your breast milk. You and your healthcare provider should decide if you will breastfeed while taking VIBATIV

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. VIBATIV and other medicines can affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a blood thinner
- medicine to control your heart rate or rhythm (antiarrhythmics)
- water pills (diuretics)
- a Non-Steroidal Anti-Inflammatory Drug (NSAID)
- certain blood pressure medicines called ACE Inhibitors or ARBs

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive VIBATIV?

- VIBATIV is injected into your vein (IV infusion) by your healthcare provider slowly over 1 hour, 1 time a day, for 7 to 14 days.
- Do not stop taking VIBATIV unless your healthcare provider tells you to even if you feel better.
- It is important that you receive **all of your VIBATIV doses**. Do not skip any doses.
- If you miss a dose or stop taking VIBATIV before getting all of your doses, contact your healthcare provider right away.
- If you skip doses or stop treatment too soon, the germs (bacteria) may grow again and VIBATIV may not work.
- Your healthcare provider will do tests before you start and while you take VIBATIV.

What are the possible side effects of VIBATIV?

VIBATIV may cause serious side effects, including:

See **"What is the most important information I should know about VIBATIV?"**

- **Kidney problems**
- **Infusion-related reactions.** Infusion-related reactions can include: red color (flushing) to your upper body, hives (raised bumps), itching or rash if VIBATIV is given too fast
- **Intestine infection.** Intestine infections can cause diarrhea or bloody stools, stomach cramps, and a fever. These infections can happen 2 or more months after you stop taking VIBATIV
- **Irregular heartbeat.**
- **Changes in blood and urine test.** Tell your healthcare provider if you plan to have any test of your blood or urine while taking VIBATIV

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of VIBATIV include:

- change in your sense of taste
- nausea
- vomiting
- foamy urine

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of VIBATIV. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store VIBATIV?

- Store VIBATIV in the original package
- Keep VIBATIV refrigerated between 35^0F to 46^0F (2^0C to 8^0C)
- Keep out of heat

Keep VIBATIV and all medicines out of the reach of children.

General Information about the safe and effective use of VIBATIV.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIBATIV for a condition for which it is not prescribed. Do not give VIBATIV to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about VIBATIV. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VIBATIV that is written for health professionals.

For more information, go to www.vibativ.com or call 1-800-727-7003.

What are the ingredients in VIBATIV?

Active ingredient: telavancin hydrochloride

Inactive ingredients: hydroxypropylbetadex, Ph. Eur (hydroxypropyl-beta-cyclodextrin), mannitol, sodium hydroxide, and hydrochloric acid

Manufactured for:	**Marketed by:**
Theravance, Inc.	Astellas Pharma US, Inc.
South San Francisco, CA 94080	Deerfield, IL 60015

VIBATIV is a trademark of Astellas Pharma Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration

August 2009

NDA 22-110 VIBATIV™ (telavancin)

[Lipoglycopeptide]

Theravance, Inc.
901 Gateway Boulevard, South San Francisco, CA 94080
[650-808-6076]

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goal of the VIBATIV REMS is to avoid unintended exposure of pregnant women to VIBATIV by:

- Educating healthcare professionals (HCPs) and patients on the potential risk of fetal developmental toxicity if women are exposed to VIBATIV while pregnant.
- Informing HCPs that a serum pregnancy test should be performed before initiating therapy with VIBATIV in women of childbearing potential.
- Informing HCPs that women of childbearing potential, including those being treated in the outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during VIBATIV use.
- Informing HCPs and patients about the Pregnancy Registry for patients exposed to VIBATIV during pregnancy.

II. REMS ELEMENTS

A. Medication Guide

Theravance will ensure that a Medication Guide will be distributed with each VIBATIV prescription in accordance with 21 CFR 208.24. VIBATIV is packaged as a single unit of use and the Medication Guide is inserted inside the carton.

Additional copies of the Medication Guide will also be available via sales and/or clinical representatives, the product website, and by request at 1-800-727-7003.

Please see appended Medication Guide.

B. Communication Plan

In accordance with FDCA 505-1(e)(3), Theravance will implement a communication plan to targeted healthcare providers and pharmacists to support the implementation of the VIBATIV REMS. The communication plan consists of the following:

1. A Dear Healthcare Provider (HCP) Letter describing the fetal effects of VIBATIV seen in animals and pregnancy prevention measures. The letter will include Pregnancy Registry Information. The letter will be accompanied by the VIBATIV Package Insert (PI) and the Medication Guide.

2. The Dear HCP Letter will be distributed to targeted HCPs and pharmacists at the specified timeframes:

    a. Prior to commercial distribution
    b. 6 months after product approval
    c. 1 and 2 years after product approval

3. The Dear HCP Letter will be distributed either through hardcopy mailings by U.S. mail or email to reach the target audience. The letter will also be available on the product website. The website will also include information about the Pregnancy Registry and the toll-free number to call to enroll in the Registry.

    The email will target physicians based on the American Medical Association database. The email distribution list for other healthcare providers will be based on other databases and secured through a private contractor.

    Providers that have an email address on file will receive the Dear HCP Letter via email. If the intended recipient does not open the Dear HCP Letter within 72 hours, the materials will be distributed hardcopy via U.S. mail. The healthcare providers on the target audience list who do not have an email on file will receive a hardcopy via U.S. mail.

    All distributions, hardcopy and electronic will include the designation "Important Drug Warning" according to 21 CFR 200.5.

4. The Dear HCP Letter will be sent to the following targeted Healthcare Providers:

    Physician Groups
    Infectious Disease
    Emergency Medicine
    Critical Care Medicine
    Hospitalist
    General Surgery
    Obstetrics and Gynecology
    Family Practice

    Other Healthcare Professionals
    Health System Pharmacists / Hospital Pharmacists
    Outpatient Infusion Providers

    Organizational Headquarters
    Infectious Disease Society of America
    American College of Emergency Physicians

Society of Critical Care Medicine
Society of Hospital Medicine
Surgical Infection Society
American Thoracic Society (critical care)
American College of Chest Physicians (critical care)
American College of Obstetrics and Gynecology
American Society of Health System Pharmacists
Society of Infectious Disease Pharmacists
American College of Clinical Pharmacists
Outpatient Parenteral Antimicrobial Therapy
American Medical Association

The Dear HCP Letter will be distributed with the VIBATIV Package Insert and Medication Guide.

Please see appended Dear HCP Letter.

C. **Elements to Assure Safe Use**

VIBATIV can be approved without any elements to assure safe use.

D. **Implementation System**

VIBATIV can be approved without any elements to assure safe use, therefore an implementation system is not required.

E. **Timetable for Submission of Assessments**

Theravance will submit REMS Assessments at 18 months, 3 years, and 7 years following the approval of the REMS (see table below). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Theravance will submit each assessment so that it will be received by the FDA on or before the due date.

Timetable for Submission of Assessments	
Assessment	Month/Year of Submission
1st Assessment (18 months from approval)	March 2011
2nd Assessment (3 years from approval)	September 2012
3rd Assessment (7 years from approval)	September 2016

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22110	ORIG-1	THERAVANCE INC	TELAVANCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
09/11/2009

APPENDIX B

Copy of U.S. Patent No. 6,635,618 B2

Patent Term Extension Application

for

U.S. Patent No. 6,635,618 B2

(Attorney Docket No. P-088-US1)

US006635618B2

(12) **United States Patent**
Leadbetter et al.

(10) **Patent No.: US 6,635,618 B2**
(45) **Date of Patent: Oct. 21, 2003**

(54) **GLYCOPEPTIDE PHOSPHONATE DERIVATIVES**

(75) Inventors: **Michael R. Leadbetter**, San Leandro, CA (US); **Martin S. Linsell**, San Mateo, CA (US)

(73) Assignee: **Theravance, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 88 days.

(21) Appl. No.: **09/847,042**

(22) Filed: **May 1, 2001**

(65) **Prior Publication Data**

US 2002/0022590 A1 Feb. 21, 2002

Related U.S. Application Data

(60) Provisional application No. 60/213,410, filed on Jun. 22, 2000.

(51) **Int. Cl.**[7] **A61K 38/14**; C07K 9/00
(52) **U.S. Cl.** **514/7**; 514/8; 530/322
(58) **Field of Search** 514/7, 8, 9, 10, 514/11; 530/317, 322, 333

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Primary Examiner—Jeffrey E. Russel
(74) *Attorney, Agent, or Firm*—Jeffrey A. Hagenah; David E. Boone

(57) **ABSTRACT**

Disclosed are glycopeptides that are substituted with one or more substituents each comprising one or more phosphono groups; and pharmaceutical compositions containing such glycopeptide derivatives. The disclosed glycopeptide derivatives are useful as antibacterial agents.

31 Claims, No Drawings

GLYCOPEPTIDE PHOSPHONATE DERIVATIVES

PRIORITY OF INVENTION

This application claims priority to U.S. Provisional Application No. 60/213410, filed Jun. 22, 2000, which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention is directed to novel phosphonate derivatives of glycopeptide antibiotics and related compounds. This invention is also directed to pharmaceutical compositions containing such glycopeptide phosphonate derivatives, methods of using such glycopeptide phosphonate derivatives as antibacterial agents, and processes and intermediates useful for preparing such glycopeptide phosphonate derivatives.

2. Background

Glycopeptides (e.g. dalbaheptides) are a well-known class of antibiotics produced by various microorganisms (see *Glycopeptide Antibiotics,* edited by R. Nagarajan, Marcel Dekker, Inc. New York (1994)). These complex multi-ring peptide compounds are very effective antibacterial agents against a majority of Gram-positive bacteria. Although potent antibacterial agents, the glycopeptides antibiotics are not used in the treatment of bacterial diseases as often as other classes of antibiotics, such as the semi-synthetic penicillins, cephalosporins and lincomycins, due to concerns regarding toxicity.

In recent years, however, bacterial resistance to many of the commonly-used antibiotics has developed (see J. E. Geraci et al., *Mayo Clin. Proc.* 1983, 58, 88–91; and M. Foldes, *J. Antimicrob. Chemother.* 1983, 11, 21–26). Since glycopeptide antibiotics are often effective against these resistant strains of bacteria, glycopeptides such as vancomycin have become the drugs of last resort for treating infections caused by these organisms. Recently, however, resistance to vancomycin has appeared in various microorganisms, such as vancomycin-resistant enterococci (VRE), leading to increasing concerns about the ability to effectively treat bacterial infections in the future (see Hospital Infection Control Practices Advisory Committee, *Infection Control Hospital Epidemiology,* 1995, 17, 364–369; A. P. Johnson et al., *Clinical Microbiology Rev,* 1990, 3, 280–291; G. M. Eliopoulos, *European J. Clinical Microbiol., Infection Disease,* 1993, 12, 409–412; and P. Courvalin, *Antimicrob. Agents Chemother,* 1990, 34, 2291–2296).

A number of derivatives of vancomycin and other glycopeptides are known in the art. For example, see U.S. Pat. Nos. 4,639,433; 4,643,987; 4,497,802; 4,698,327; 5,591,714; 5,840,684; and 5,843,889. Other derivatives are disclosed in EP 0 802 199; EP 0 801 075; EP 0 667 353; WO 97/28812; WO 97/38702; WO 98/52589; WO 98/52592; and in *J. Amer. Chem. Soc.,* 1996, 118, 13107–13108; *J. Amer. Chem. Soc.,* 1997, 119, 12041–12047; and *J. Amer. Chem. Soc.,* 1994, 116, 4573–4590.

Despite the above referenced disclosures, a need currently exists for novel glycopeptide derivatives having effective antibacterial activity and an improved mammalian safety profile. In particular, a need exists for glycopeptide derivatives which are effective against a wide spectrum of pathogenic microorganism, including vancomycin-resistant microorganisms, and which have reduced tissue accumulation and/or nephrotoxicity.

SUMMARY OF THE INVENTION

The present invention provides novel glycopeptide phosphonate derivatives having highly effective antibacterial activity and an improved mammalian safety profile. More specifically, the glycopeptide phosphonate derivatives of the invention unexpectedly exhibit reduced tissue accumulation and/or nephrotoxicity when administered to a mammal.

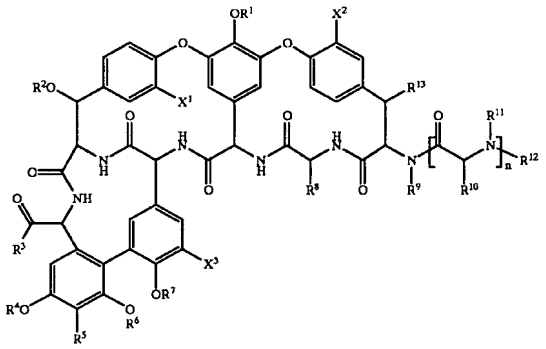
Accordingly, this invention provides glycopeptide compounds substituted with one or more (e.g., 1, 2 or 3) substituents comprising one or more (e.g., 1, 2 or 3) phosphono (—PO_3H_2) groups; or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof. Preferably, the glycopeptide compound is substituted with one or two substituents comprising one or two phosphono groups. More preferably, the glycopeptide compound is substituted with one substituent comprising one or two phosphono groups, preferably one phosphono group. Optionally, the glycopeptide compounds of this invention may also be substituted with other substituents not comprising a phosphono group, provided that at least one substituent comprises one or more phosphono groups.

Accordingly, in one preferred embodiment, this invention provides a glycopeptide compound substituted at the C-terminus with a substituent comprising one or two phosphono (—PO_3H_2) groups; or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof. Preferably, the phosphono-containing substituent is attached to the carbonyl group at the C-terminus through an amide bond, an ester bond, or a thioester bond; more preferably, through an amide bond. Preferably, the phosphono-containing substituent comprises one phosphono group. Particularly preferred phosphono-containing substituents at the C-terminus include phosphonomethylamino, 3-phosphonopropylamino and 2-hydroxy-2-phosphonoethylamino.

In another preferred embodiment, this invention provides a glycopeptide compound substituted at the R-terminus (on the resorcinol ring) with a substituent comprising one or two phosphono (—PO_3H_2) groups; or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof. Preferably, the phosphono-containing substituent is attached to the R-terminus (i.e., the resorcinol ring) through the nitrogen atom of an aminomethyl group attached to the R-terminus. Preferably, the phosphono-containing substituent comprises one phosphono group. Particularly preferred phosphono-containing substituents at the R-terminus include N-(phosphonomethyl)aminomethyl; -(2-hydroxy-2-phosphonoethyl)aminomethyl; N-carboxymethyl-N-(phosphonomethyl)aminomethyl; N,N-bis (phosphonomethyl)aminomethyl; and N-(3-phosphonopropyl)aminomethyl.

In still another preferred embodiment, this invention provides a glycopeptide compound substituted at the C-terminus and at the R-terminus with a substituent comprising one or two phosphono (—PO_3H_2) groups; or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof. Preferably, the phosphono-containing substituents each comprises one phosphono group.

A preferred compound of the invention is a glycopeptide of formula I:



wherein:

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $—R^a—Y—R^b—(Z)_x$; or R^1 is a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$;

R^2 is hydrogen or a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$;

R^3 is $—OR^c$, $—NR^cR^c$, $—O—R^a—Y—R^b—(Z)_x$, $—NR^c—R^a—Y—R^b—(Z)_x$, $—NR^cR^e$, or $—O—R^e$; or R^3 is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $—R^a—Y—R^b—(Z)_x$, $—C(O)R^d$ and a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$, or R^4 and R^5 can be joined, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with $—NR^c—R^a—Y—R^b—(Z)_x$;

R^5 is selected from the group consisting of hydrogen, halo, $—CH(R^c)—NR^cR^c$, $—CH(R^c)—NR^cR^e$, $—CH(R^c)—NR^c—R^a—Y—R^b—(Z)_x$, $—CH(R^c)—R^x$, $—CH(R^c)—NR^c—R^a—C(=O)—R^x$, and a substituent that comprises one or more phosphono groups;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $—R^a—Y—R^b—(Z)_x$, $—C(O)R^d$ and a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$, or R^5 and R^6 can be joined, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with $—NR^c—R^a—Y—R^b—(Z)_x$;

R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $—R^a—Y—R^b—(Z)_x$, and $—C(O)R^d$;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $—Ar^1—O—Ar^2—$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;

R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $—C(O)R^d$, $—C(NH)R^d$, $—C(O)NR^cR^c$, $—C(O)OR^d$, $—C(NH)NR^cR^c$, $—R^a—Y—R^b—(Z)_x$, and $—C(O)—R^a—Y—R^b—(Z)_x$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $—OR^{14}$;

R^{14} is selected from hydrogen, $—C(O)R^d$ and a saccharide group;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $—C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

each R^f is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, or heterocyclic;

R^x is an N-linked amino saccharide or an N-linked heterocycle;

X^1, X^2 and X^3 are independently selected from hydrogen or chloro;

each Y is independently selected from the group consisting of oxygen, sulfur, $—S—S—$, $—NR^c—$, $—S(O)—$, $—SO_2—$, $—NR^cC(O)—$, $—OSO_2—$, $—OC(O)—$, $—NR^cSO_2—$, $—C(O)NR^c—$, $—C(O)O—$,

—SO_2NR^c—, —SO_2O—, —P(O)(OR^c)O—, —P(O)(OR^c)NR^c—, —OP(O)(OR^c)O—, —OP(O)(OR^c)NR^c—, —OC(O)O—, —NR^cC(O)O—, —NR^cC(O)NR^c—, —OC(O)NR^c—, —C(=O)—, and —$NR^cSO_2NR^c$—;

each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2; and

x is 1 or 2;

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof;

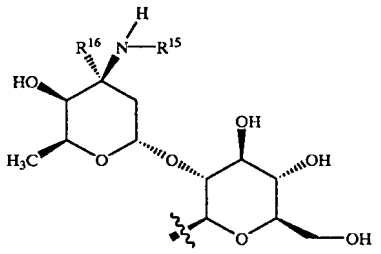
provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.

A preferred compound of the invention is a compound of formula I wherein: R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and —R^a—Y—R^b—$(Z)_x$; or R^1 is a saccharide group optionally substituted with —R^a—Y—R^b—$(Z)_x$, R^f, —C(O)R^f, or —C(O)—R^a—Y—R^b—$(Z)_x$; R^2 is hydrogen or a saccharide group optionally substituted with —R^a—Y—R^b—$(Z)_x$, R^f, —C(O)R^f, or —C(O)—R^a—Y—R^b—$(Z)_x$; R^3 is —OR^c, —NR^cR^c, —O—R^a—Y—R^b—$(Z)_x$, —NR^c—R^a—Y—R^b—$(Z)_x$, —NR^cR^e, or —O—R^e; or R^3 is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups; R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, —R^a—Y—R^b—$(Z)_x$, —C(O)R^d and a saccharide group optionally substituted with —R^a—Y—R^b—$(Z)_x$, R^f, —C(O)R^f, or —C(O)—R^a—Y—R^b—$(Z)_x$; R^5 is selected from the group consisting of hydrogen, halo, —CH(R^c)—NR^cR^c, —CH(R^c)—NR^cR^e, —CH(R^c)—NR^c—R^a—Y—R^b—$(Z)_x$, —CH(R^c)—R^x, —CH(R^c)—NR^c—R^a—C(=O)—R^x, and a substituent that comprises one or more phosphono groups; R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, —R^a—Y—R^b—$(Z)_x$, —C(O)R^d and a saccharide group optionally substituted with —NR^c—R^a—Y—R^b—$(Z)_x$, or R^5 and R^6 can be joined, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with —NR^c—R^a—Y—R^b—$(Z)_x$; R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, —R^a—Y—R^b—$(Z)_x$, and —C(O)R^d; R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form —Ar^1—O—Ar^2—, where Ar^1 and Ar^2 are independently arylene or heteroarylene; R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring; R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, —C(O)R^d, —C(NH)R^d, —C(O)NR^cR^c, —C(O)OR^d, —C(NH)NR^cR^c and —Ra—Y—R^b—$(Z)_x$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring; R^{13} is selected from the group consisting of hydrogen or —OR^{14}; R^{14} is selected from hydrogen, —C(O)R^d and a saccharide group; each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene; each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen; each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and —C(O)R^d; each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; R^e is a saccharide group; each R^f is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, or heterocyclic; R^x is an N-linked amino saccharide or an N-linked heterocycle; X^1, X^2 and X^3 are independently selected from hydrogen or chloro; each Y is independently selected from the group consisting of oxygen, sulfur, —S—S—, —NR^c—, —S(O)—, —SO_2—, —NR^cC(O)—, —OSO_2—, —OC(O)—, —NR^cSO_2—, —C(O)NR^c—, —C(O)O—, —SO_2NR^c—, —SO_2O—, —P(O)(OR^c)O—, —P(O)(OR^c)NR^c—, —OP(O)(OR^c)O—, —OP(O)(OR^c)NR^c—, —OC(O)O—, —NR^cC(O)O—, —NR^cC(O)NR^c—, —OC(O)NR^c—, —C(=O)—, and —$NR^cSO_2NR^c$—; each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic; n is 0, 1 or 2; and x is 1 or 2; or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof; provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.

Preferably, R^1 is a saccharide group optionally substituted with —R^a—Y—R^b—$(Z)_x$, R^f, —C(O)R^f, or —C(O)—R^a—Y—R^b—(Z). More preferably R^1 is a saccharide group substituted on the saccharide nitrogen with —CH_2CH_2—NH—$(CH_2)_9CH_3$; —$CH_2CH_2CH_2$—NH—$(CH_2)_8CH_3$; —$CH_2CH_2CH_2CH_2$—NH—$(CH_2)_7CH_3$; —CH_2CH_2—NHSO_2—$(CH_2)_9CH_3$; —CH_2CH_2—NHSO_2—$(CH_2)_{11}CH_3$; —CH_2CH_2—S—$(CH_2)_8CH_3$; —CH_2CH_2—S—$(CH_2)_9CH_3$; —CH_2CH_2—S—$(CH_2)_{10}CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_8CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_9CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_3$—CH=CH—$(CH_2)_4CH_3$ (trans); —$CH_2CH_2CH_2CH_2$—S—$(CH_2)_7CH_3$; —CH_2CH_2—S(O)—$(CH_2)_9CH_3$; —CH_2CH_2—S—$(CH_2)_6Ph$; —CH_2CH_2—S—$(CH_2)_8Ph$; —$CH_2CH_2CH_2$—S—$(CH_2)_8Ph$; —CH_2CH_2—NH—CH_2-4-(4-Cl—Ph)—Ph; —CH_2CH_2—NH—CH_2-4-[4-$(CH_3)_2CHCH_2$—]—Ph; —CH_2CH_2—NH—CH_2-4-(4-CF_3—Ph)—Ph; —CH_2CH_2—S—CH_2-4-(4-Cl—Ph)—Ph; —CH_2CH_2—S(O)—CH_2-4-(4-Cl—Ph)-Ph; —$CH_2CH_2CH_2$—S—CH_2-4-

(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S(O)—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S—CH_2-4-[3,4-di-Cl—$PhCH_2O$—)—Ph; —CH_2CH_2—$NHSO_2$—CH_2-4-[4-(4-Ph)—Ph]—Ph; —$CH_2CH_2CH_2$—$NHSO_2$—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—$NHSO_2$—CH_2-4-(Ph—C≡C—)—Ph; —$CH_2CH_2CH_2$—$NHSO_2$-4-(4-Cl—Ph)—Ph; or —$CH_2CH_2CH_2$—$NHSO_2$-4-(naphth-2-yl)—Ph. Preferably R^1 is also a saccharide group substituted on the saccharide nitrogen with a 4-(4-chlorophenyl)benzyl group or with a 4-(4-chlorobenzyloxy)benzyl group.

In a preferred embodiment, R^1 is a saccharide group of the formula:



wherein R^{15} is —R^a—Y—R^b—$(Z)_x$, R^f, —C(O)R^f, or —C(O)—R^a—Y—R^b—$(Z)_x$; and R^{16} is hydrogen or methyl.

Preferably, R^{15} is —CH_2CH_2—NH—$(CH_2)_9CH_3$; —$CH_2CH_2CH_2$—NH—$(CH_2)_8CH_3$; —$CH_2CH_2CH_2CH_2$—NH—$(CH_2)_7CH_3$; —CH_2CH_2—$NHSO_2$—$(CH_2)_9CH_3$; —CH_2CH_2—$NHSO_2$—$(CH_2)_{11}CH_3$; —CH_2CH_2—S—$(CH_2)_8CH_3$; —CH_2CH_2—S—$(CH_2)_9CH_3$; —CH_2CH_2—S—$(CH_2)_{10}CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_8CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_9CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_3$—CH=CH—$(CH_2)_4CH_3$ (trans); —$CH_2CH_2CH_2CH_2$—S—$(CH_2)_7CH_3$; —CH_2CH_2—S(O)—$(CH_2)_9CH_3$; —CH_2CH_2—S—$(CH_2)_6Ph$; —CH_2CH_2—$(CH_2)_8Ph$; —$CH_2CH_2CH_2$—S—$(CH_2)_8Ph$; —CH_2CH_2—NH—CH_2-4-(4-Cl—Ph)—Ph; —CH_2CH_2—NH—CH_2-4-[4-$(CH_3)_2CHCH_2$—]—Ph; —CH_2CH_2—NH—CH_2-4-(4-CF_3-Ph)—Ph; —CH_2CH_2—S—CH_2-4-(4-Cl—Ph)—Ph; —CH_2CH_2—S(O)—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S(O)—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S—CH_2-4-[3,4-di-Cl—$PhCH_2O$—)—Ph; —CH_2CH_2—$NHSO_2$—CH_2-4-[4-(4-Ph)—Ph]—Ph; —$CH_2CH_2CH_2$—$NHSO_2$—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—$NHSO_2$—CH_2-4-(Ph-C≡C—)—Ph; —$CH_2CH_2CH_2$—$NHSO_2$-4-(4-Cl—Ph)—Ph; or —$CH_2CH_2CH_2$—$NHSO_2$-4-(naphth-2-yl)—Ph. Preferably R^{15} can also be a 4-(4-chlorophenyl)benzyl group or a 4-(4-chlorobenzyloxy)benzyl group.

Preferably, R^2 is hydrogen.

Preferably, R^3 is —OR^c; —NR^cR^c; or a nitrogen-linked, oxygen-linked, or sulfur-linked substituent comprising one or two phosphono groups, or a pharmaceutically acceptable salt thereof. When R^3 is a phosphono-containing substituent, R^3 is preferably a nitrogen-linked substituent comprising one phosphono group, or a pharmaceutically acceptable salt thereof. Preferably, R^3 is a group of the formula —O—R^a—$P(O)(OH)_2$, —S—R^a—$P(O)(OH)_2$, or —NR^c—R^a—$P(O)(OH)_2$. More preferably, R^3 is a group of the formula —NH—R^a—$P(O)(OH)_2$, where R^a is as defined herein. In this formula, R^a is preferably an alkylene group. Particularly preferred R^3 substituents include phosphonomethylamino, 3-phosphonopropylamino and 2-hydroxy-2-phosphonoethylamino groups and the like.

Preferably, when R^3 is not a phosphono-containing substituent, R^3 is —OH; —NH—$(CH_2)_3$—$N(CH_3)_2$; N-(D-glucosamine); —NHCH$(CO_2CH_3)CH_2CO_2CH_3$; —NH$(CH_2)_3$—(morpholin-4-yl); —NH$(CH_2)_3$—NH$(CH_2)_2CH_3$; —NH$(CH_2$-piperidin-1-yl; —NH$(CH_2)_4NHC(N)NH_2$; —NH$(CH_2)_2$—$N^+(CH_3)_3$; —NHCH(COOH)$(CH_2)_3NHC/]N)NH_2$; —NH—[$CH_2CH_2CH_2$—NH—]$_3$—H; —N[$(CH_2)_3N(CH_3)_2]_2$; —NH$(CH_2)_3$-imidazol-1-yl; —NHCH_2-4-pyridyl; —NH$(CH_2)_3CH_3$; —NH$(CH_2)_2OH$; —NH$(CH_2)_5OH$; —NH$(CH_2)_2OCH_3$; —NHCH_2—tetrahydrofuran-2-yl; —N[$(CH_2)_2OH]_2$; —NH$(CH_2)_2$N[$(CH_2)_2OH]_2$; ——NHCH_2COOH; —NHCH(COOH)CH_2OH; —NH$(CH_2)_2COOH$; N-(glucamine); —NH$(CH_2)_2COOH$; —NH$(CH_2)_3SO_3H$; —NHCH(COOH)$(CH_2)_2NH_2$; —NHCH(COOH)$(CH_2)_3NH_2$; —NHCH(COOH)$CH_2CO_2(CH_2)_3$—$N^+(CH_3)_3$; —NHCH(COOH)$CH_2CO_2(CH_2)_2C(O)$—$N(CH_3)_2$; —NHCH(COOH)$CH_2CO_2(CH_2)_3$-morpholin-4-yl; —NHCH(COOH)$CH_2CO_2(CH_2)_2OC(O)C(CH_3)_3$; —NHCH($CH_2COOH$)$CO_2(CH_2)_3$—$N^+(CH_3)_3$; —NHCH($CH_2COOH$)$CO_2(CH_2)_2C(O)N(CH_3)_2$; or —NHCH($CH_2COOH$)$CO_2(CH_2)_3$-morpholin-4-yl. —NHCH($CH_2COOH$)$CO_2(CH_2)_2OC(O)C(CH_3)_3$; —NHCH(COOH)$CH_2CO_2CH_3$; —NHCH($CH_2COOH$)$CO_2(CH_2)_2N(CH_3)_2$; —NHCH(COOH)$CH_2CO_2CH_2C(O)N(CH_3)_2$; —NHCH($CH_2COOH$)$CO_2CH_2C(O)N(CH_3)_2$; —NHCH($CH_2COOH$)$CO_2CH_3$; —NH$(CH_2)_3N(CH_3)_2$; —NH$CH_2CH_2CO_2CH_3$; —NHCH[$CH_2CO_2CH_2C(O)N(CH_3)_2$]$CO_2CH_2$—C(O)—$N(CH_3)_2$; —NH$CH_2CO_2CH_3$; —N-(methyl 3-amino-3-deoxyaminopyranoside); -N-(methyl 3-amino-2,3,6-trideoxyhexopyranoside); -N-(2-amino-2-deoxy-6-(dihydrogenphosphate)glucopyranose; —N-(2-amino-2-deoxygluconic acid); —NH$(CH_2)_4COOH$; —N—(N—CH_3-D-glucamine; —NH$(CH_2)_6COOH$; —O(D-glucose); —NH$(CH_2)_3OC(O)CH(NH_2)CH_3$; —NH$(CH_2)_4CH(C(O)$-2-HOOC-pyrrolidin-1-yl)NHCH(COOH)—CH_2CH_2Ph (S,S isomer); —NH—CH_2CH_2—NH—$(CH_2)_9CH_3$; —NH$(CH_2)C(O)CH_2C(O)N(CH_3)_2$;

Preferably, R^4, R^6 and R^7 are each independently selected from hydrogen or —C(O)R^d. More preferably, R^4, R^6 and R^7 are each hydrogen.

Preferably, R^5 is hydrogen, —CH_2—NHR^e, —CH_2—NR^eR^e, —CH_2—NH—R^a—Y—R^b—$(Z)_x$, or a substituent comprising one or two phosphono groups. When R^5 is a substituent comprising a phosphono group, R^5 is preferably a group of the formula —$CH(R^{21})$—$N(R^c)$—R^a—$P(O)(OH)_2$ wherein R^{21} is hydrogen or R^d, preferably hydrogen, and R^a, R^c, and R^d, are as defined herein. More preferably, when R^5 is phosphono-containing substituent, R^5 is preferably a group of the formula —CH_2—NH—R^a—$P(O)(OH)_2$, where R^a is as defined herein. In this formula, R^a is preferably an alkylene group; more preferably, an alkylene group containing from 2 to about 6 carbon atoms.

Particularly preferred R^5 substituents include N-(phosphonomethyl)-aminomethyl; N-(2-hydroxy-2-phosphonoethyl)aminomethyl; N-carboxymethyl-N-(2-phosphonoethyl)aminomethyl; N,N-bis(phosphonomethyl)-aminomethyl; and N-(3-phosphonopropyl)aminomethyl; and the like.

Preferably, when R^5 is not a phosphono-containing Substituent, R^5 is hydrogen, —CH_2—NHR^e, —CH_2—NR^eR^e— or —CH_2—NH—R^a—Y—R^b—$(Z)_x$, R^5 can also preferably be hydrogen; —CH_2—N—(N—CH_3-D-glucamine); —CH_2—NH—CH_2CH_2—NH—$(CH_2)_9CH_3$; —CH_2—NH—CH_2CH_2—NHC(O)—$(CH_2)_3COOH$; —CH_2—NH—$(CH_2)_9CH_3$;—CH_2—NH—CH_2CH_2—COOH; —CH_2—NH—$(CH_2)_5COOH$; —CH_2-(morpholin-4-yl); —CH_2—NH—CH_2CH_2—O—CH_2OH; —CH_2—

NH—$CH_2CH(OH)$—CH_2OH; —CH_2—$N[CH_2CH_2OH]_2$; —CH_2—NH—$(CH_2)_3$—$N(CH_3)_2$; —CH_2—$N[(CH_2)_3$—$N(CH_3)_2]_2$; —CH_2—NH—$(CH_2)_3$-(imidazol-1-yl); —CH_2—NH—$(CH_2)_3$—(morpholin-4-yl); —CH_2—NH—$(CH_2)_4$—$NHC(NH)NH_2$; —CH_2—N—(2-amino-2-deoxygluconic acid); —CH_2—NH—CH_2CH_2—NH—$(CH_2)_{11}CH_3$; —CH_2—NH—CH(COOH)CH_2COOH; —CH_2—NH—CH_2CH_2—$NHSO_2$—$(CH_2)_7CH_3$; —CH_2—NH—CH_2CH_2—$NHSO_2$—$(CH_2)_8CH_3$; CH_2—NH—CH_2CH_2—$NHSO_2$—$(CH_2)_9CH_3$; —CH_2—NH—CH_2CH_2—$NHSO_2$—$(CH_2)_3$; —CH_3; —CH_2—NH—11CH_3; —CH_2—NH—CH_2CH_2—NH—$(CH_2)_7CH_3$; —CH_2—NH—CH_2CH_2—O—CH_2 CH_2OH; —CH_2—NH—CH_2CH_2C(O)—N-(D-glucosamine); —CH_2—NH—(6-oxo-[1,3]oxazinan-3-yl); —CH_2—NH—CH_2CH_2—S—$(CH_2)_7CH_3$; —CH_2—NH—CH_2CH_2—S—$(CH_2)_8CH_3$; —CH_2—NH—CH_2—S—$(CH_2)_9CH_3$; —CH_2—NH—CH_2CH_2—S—$(CH_2)_{11}CH_3$; —CH_2—NH—CH_2CH_2—S—$(CH_2)_6Ph$; —CH_2—NH—CH_2CH_2—S—$(CH_2)_8Ph$; —CH_2—NH—CH_2CH_2—S—$(CH_2)_{10}Ph$; —CH_2—NH—CH_2CH_2—S—CH_2—(4-(4-(CF_3—Ph)Ph); —CH_2—NH—CH_2CH_2—NH—$(CH_2)_{11}CH_3$; or —CH_2—NH—$(CH_2)_5$—COOH.

Preferably, R^8 is —$CH_2C(O)NH_2$, —CH_2COOH, benzyl, 4-hydroxyphenyl or 3-chloro-4-hydroxyphenyl.

Preferably, R^9 is hydrogen or alkyl.

Preferably, R^{10} is alkyl or substituted alkyl. More preferably, R^{10} is the side-chain of a naturally occurring amino acid, such as isobutyl.

Preferably, R^{11} is hydrogen or alkyl.

Preferably, R^{12} is hydrogen, alkyl, substituted alkyl or —$C(O)R^d$. R^{12} can also preferably be hydrogen; —CH_2COOH; —CH_2—$[CH(OH)]_5CH_2OH$; —$CH_2CH(OH)CH_2OH$; —$CH_2CH_2NH_2$; —$CH_2C(O)OCH_2CH_3$; —CH_2-(2-pyridyl); —CH_2-$[CH(OH)]_4COOH$; —CH_2; (3—carboxyphenyl); (R)—$C(O)CH(NH_2)(CH_2)_4NH_2$; —C(O)Ph; —$C(O)CH_2NHC(O)CH_3$; E—CH_2CH_2—S—$(CH_2)_3CH$=$CH(CH_2)_4CH_3$; or —$C(O)CH_3$.

Preferably, X^1 and X^2 are each chloro.

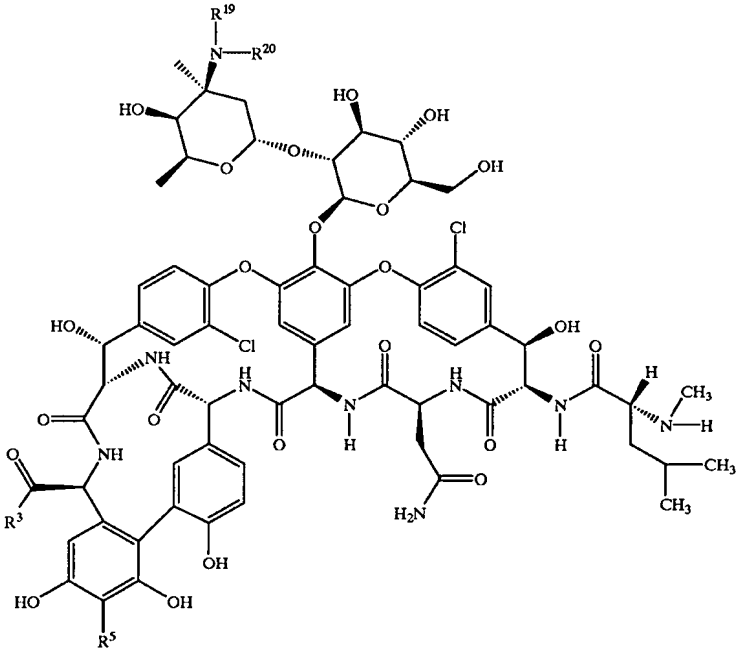
Preferably, X^3 is hydrogen.

Preferably, each Y is independently selected from the group consisting of oxygen, sulfur, —S—S—, —NR^c—, —S(O)—, —SO_2—, —$NR^cC(O)$—, —OSO_2—, —OC(O)—, —NR^cSO_2—, —$C(O)NR^c$—, —C(O)O—, —SO_2NR^c—, —SO_2O—, —P(O)(OR^c)O—, —P(O)(OR^c)NR^c—, —OP(O)(OR^c)O—, —OP(O)(OR^c)NR^c—, —OC(O)O—, —$NR^cC(O)O$—, —$NR^cC(O)NR^c$—, —OC(O)NR^c—, and —$NR^cSO_2NR^c$—.

Preferably, n is 0 or 1, and more preferably, n is 1.

Another preferred compound of the invention is a glycopeptide of formula II:

(II)



wherein:

R^{19} is hydrogen;

R^{20} is —R^a—Y—R^b—$(Z)_x$, R^f, —$C(O)R^f$, or —C(O)—R^a—Y—R^b—$(Z)_x$; and

R^a, Y, R^b, Z, x, R^f, R^3, and R^5 have any of the values or preferred values described herein;

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof,

provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.

Preferably, R^{20} is —CH_2CH_2—NH—$(CH_2)_9CH_3$; —$CH_2CH_2CH_2$—NH—$(CH_2)_8CH_3$; —$CH_2CH_2CH_2CH_2$—NH—$(CH_2)_7CH_3$; —CH_2CH_2—$NHSO_2$—$(CH_2)_9CH_3$; —CH_2CH_2—$NHSO_2$—$(CH_2)_{11}CH_3$; —CH_2CH_2—S—$(CH_2)_8CH_3$; —CH_2CH_2—S—$(CH_2)_9CH_3$; —CH_2—S—$(CH_2)_{10}CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_8CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_9CH_3$; —$CH_2CH_2CH_2$—S—$(CH_2)_3$; CH=CH—$(CH_2)_4CH_3$ (trans); —$CH_2CH_2CH_2CH_2$—S—$(CH_2)_7CH_3$; —CH_2CH_2—S

(O)—$(CH_2)_9CH_3$; —CH_2CH_2—S—$(CH_2)_6$Ph; —CH_2CH_2—S—$(CH_2)_8$Ph; —$CH_2CH_2CH_2$—S—$(CH_2)_8$Ph; —CH_2CH_2—NH—CH_2-4-(4-Cl—Ph)—Ph; —CH_2CH_2—NH—CH_2-4-[4-$(CH_3)_2CHCH_2$—]—Ph; —CH_2CH_2—NH—CH_2-4-(4-CF_3—Ph)—Ph; —CH_2CH_2—S—CH_2-4-(4-Cl—Ph)—Ph; —CH_2CH_2—S(O)—CH_2-4-(4Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S(O)—CH_2-4-(4Cl—Ph)—Ph; —$CH_2CH_2CH_2$—S—CH_2-4-[3,4-di-Cl—PhCH_2O—)—Ph; —CH_2CH_2—$NHSO_2$—CH_2-4-[4-(4-Ph)—Ph]—Ph; —$CH_2CH_2CH_2$—$NHSO_2$—CH_2-4-(4-Cl—Ph)—Ph; —$CH_2CH_2CH_2$—$NHSO_2$—CH_2-4-(Ph—C≡C—)—Ph; —$CH_2CH_2CH_2$—$NHSO_2$-4-(4-Cl—Ph)—Ph; or —$CH_2CH_2CH_2$—$NHSO_2$-4-(naphth-2-yl)—Ph. Preferably R^{20} is also a 4-(4-chlorophenyl)benzyl group or a 4-(4-chlorobenzyloxy)benzyl group.

In another preferred embodiment, the invention provides a compound of formula II, wherein R^{19} is hydrogen; R^{20} is —CH_2CH_2NH—$(CH_2)_9CH_3$; R^3 is —OH; and ^{5} is a substituent comprising a phosphono group; or a pharmaceutically acceptable salt thereof.

In yet another preferred embodiment, the invention provides a compound of formula II, wherein R^{19} is hydrogen; R^{20} is —R^a—Y—R^b—$(Z)_x$, R^f, —C(O)R^f, or —C(O)—R^a—Y—R^b—$(Z)_x$; R^3 is —OH; and R^5 is —CH_2—NH—CH_2—P(O)$(OH)_2$; or a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the invention. In one preferred embodiment, the pharmaceutically acceptable carrier comprises an aqueous cyclodextrin solution. Preferably, the cyclodextrin is hydroxypropyl-β-cyclodextrin or sulfobutyl ether β-cyclodextrin. More preferably, the cyclodextrin is hydroxypropyl-β-cyclodextrin.

The compounds of the invention are highly effective antibacterial agents. Accordingly, the invention also provides a method of treating a mammal having a bacterial disease, comprising administering to the mammal a therapeutically effective amount of a compound of the invention. The invention also provides a method of treating a mammal having a bacterial disease, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition of the invention.

The invention also provides processes and intermediates useful for preparing compounds of the invention, which processes and intermediates are described further herein.

The invention also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound of the invention in the manufacture of a formulation or medicament for treating a bacterial disease in a mammal.

The invention also provides a pharmaceutical composition which comprises as an active ingredient a compound of the invention for the treatment of a bacterial disease.

The invention also provides a method for preparing a glycopeptide of the invention which is substituted at the C-terminus with a substituent that comprises one or more phosphono groups, comprising coupling a corresponding starting glycopeptide wherein the C-terminus is a carboxy group with a suitable phosphono containing compound.

The invention also provides a method for preparing a glycopeptide of the invention which is substituted at the R-terminus with a substituent that comprises one or more phosphono groups, comprising coupling a corresponding starting glycopeptide wherein the R-terminus is unsubstituted with a suitable phosphono containing compound. When the starting glycopeptide is substituted at the vancosamine amino terminus, such a method can further optionally comprise preparing the starting glycopeptide by reductively alkylating a corresponding glycopeptide wherein the vancosamine amino terminus is the corresponding amine.

The invention also provides a method for preparing a glycopeptide of the invention that is substituted at the C-terminus, comprising derivatizing a corresponding starting glycopeptide wherein the C-terminus is a carboxy group.

The invention also provides a method for preparing a glycopeptide of the invention which is substituted at the R-terminus, comprising derivatizing a corresponding starting glycopeptide wherein the R-terminus is unsubstituted (i.e. a hydrogen).

This invention also provides a method for preparing a compound of formula II, wherein R^3 is —OH, R^5 is —CH_2—NH—R^a—P(O)$(OH)_2$, R^{19} is hydrogen and R^{20} is —R^a—Y—R^b—$(Z)_x$, or —R^f, and R^a, R^b, R^f, Y, Z and x are as defined herein, or salt thereof; the method comprising:

(a) reductively alkylating a compound of formula II, wherein R^3 is —OH and R^5, R^{19} and R^{20} are hydrogen, or a salt thereof, with an aldehyde of the formula HC(O)—$R^{a'}$—Y—R^b—$(Z)_x$, or HC(O)R^f wherein $R^{a'}$ and R^f represent R^a and R^f, respectively, minus one —CH_2— group, to form a compound of formula II wherein R^3 is —OH, R^5 and R^{19} are hydrogen and R^{20} is —R^a—Y—R^b—$(Z)_x$ or —R^f, or salt thereof, and

(b) reacting the product from step (a) with formaldehyde and H_2N—R^a—P(O)$(OH)_2$ to form a compound of formula II wherein R^3 is —OH, R^5 is —CH_2NH—R^a—P(O)$(OH)_2$, R^{19} is hydrogen and R^{20} is —R^a—Y—R^b—$(Z)_x$, or —R^f, or salt thereof.

Preferred compounds of the invention are the compounds of formula II shown in Table I below wherein R^{19} is hydrogen.

TABLE I

Preferred Compounds of formula II

Compound	R^3	R^5	R^{20}
1	phosphonomethylamino	H	$CH_3(CH_2)_9NHCH_2CH_2$—
2	phosphonomethylamino	H	$CH_3(CH_2)_9OCH_2CH_2$—
3	phosphonomethylamino	H	$CH_3(CH_2)_9SCH_2CH_2$—
4	phosphonomethylamino	H	$CH_3(CH_2)_{12}$—
5	phosphonomethylamino	H	4-(4-chlorophenyl)-benzyl
6	phosphonomethylamino	H	2-(4-(4-chlorophenyl)-benzylamino)ethyl
7	phosphonomethylamino	H	4-(4'-chlorobiphenyl)-butyl
8	phosphonomethylamino	H	5-(4'-chlorobiphenyl)-pentyl

TABLE I-continued

Preferred Compounds of formula II

Compound	R^3	R^5	R^{20}
9	3-phosphonopropylamino	H	$CH_3(CH_2)_9SCH_2CH_2$—
10	2-hydroxy-2-phosphonoethylamino	H	4-(4-chlorophenyl)-benzyl
11	OH	(phosphonomethyl)-aminomethyl	$CH_3(CH_2)_9NHCH_2CH_2$—
12	OH	(phosphonomethyl)-aminomethyl	$CH_3(CH_2)_9SCH_2CH_2$—
13	OH	(phosphonomethyl)-aminomethyl	$CH_3(CH_2)_9OCH_2CH_2$—
14	OH	(phosphonomethyl)-aminomethyl	$CH_3(CH_2)_{12}$—
15	OH	(phosphonomethyl)-aminomethyl	4-(4-chlorophenyl)benzyl
16	OH	(phosphonomethyl)-aminomethyl	2-(4-(4-chlorophenyl)-benzylamino)ethyl
17	OH	(phosphonomethyl)-aminomethyl	4-(4'-chlorobiphenyl)butyl
18	OH	(phosphonomethyl)-aminomethyl	5-(4'-chlorobiphenyl)pentyl
19	OH	(phosphonomethyl)-aminomethyl	3-[4-(4-chlorobenzyloxy)-benzylthio]propyl
20	OH	N-(2-hydroxy-2-phosphonoethyl)aminomethyl	$CH_3(CH_2)_9SCH_2CH_2$—
21	OH	N-(carboxymethyl)-N-2-phosphonomethyl)-aminomethyl	$CH_3(CH_2)_9SCH_2CH_2$—
22	OH	N,N-bis(phosphono-methyl)aminomethyl	$CH_3(CH_2)_9NHCH_2CH_2$—
23	OH	3-phosphonopropyl-aminomethyl	$CH_3(CH_2)_9SCH_2CH_2$—
24	OH	3-phosphonopropyl-aminomethyl	4-(4-chlorophenyl)benzyl
25	phosphonomethylamino	—CH_2—N—(N—CH_3—D-glucamine	$CH_3(CH_2)_9NHCH_2CH_2$—
26	OH	(phosphonomethyl)-aminomethyl	—$(CH_2)_3NH$—SO_2-4-(4-chlorophenyl)phenyl

Another preferred group of compounds of the invention are phosphono derivatives of the glycopeptide antibiotic A82846B (also known as chloroorienticin A oy LY264826). See for example R. Nagarajan et al., *J. Org. Chem.,* 1988, 54, 983–986; and N. Tsuji et al., *J. Antibiot.,* 1988, 41, 819–822. The structure of this glycopeptide is similar to vancomycin, except A82846B contains an additional amino sugar (i.e. 4-epivancosamine attached at the R^2 position in formula I.) and further contains 4-epivancosamine in place of vancosamine in the disaccharide moiety attached at the R^1 position in formula I. For example, a preferred group of compounds are N-alkylated derivatives of A82846B that are substituted at the C-terminus or the R-terminus with a substituent that comprises one or more (e.g. 1, 2, 3, 4, or 5) phosphono (—PO_3H_2) groups; or a pharmaceutically acceptable salt thereof. A preferred group of compounds of the invention that are derivatives of A82846B are substituted at either the C-terminus or the R-terminus with a substituent that comprises one or more (e.g. 1, 2, 3, 4, or 5) phosphono (—PO_3H_2) groups. Another preferred group of compounds of the invention that are derivatives of A82846B are substituted at the C-terminus and the R-terminus with substituents that each comprises one or more (e.g. 1, 2, 3, 4, or 5) phosphono (—PO_3H_2) groups. Another preferred group of compounds of the invention are phosphono derivatives of A82846B having a 4-(4-chlorophenyl)benzyl group or a 4-(4-chlorobenzyloxy)benzyl group attached at the amino group of the 4-epi-vancosamine of the disaccharide moiety. The compounds of the invention that are phosphono derivatives of A82846B can readily be prepared using the procedures described herein.

The phosphono compounds of the invention have been found to unexpectedly exhibit reduced tissue accumulation and/or nephrotoxicity when administered to a mammal. While not wishing to be bound by theory, it is believed that the phosphono moiety serves to increase the overall negative charge of the glycopeptide under physiological conditions thereby facilitating excretion from the mammal after administration. The unexpected increase in excretion of the phosphono compounds of the invention may be responsible for the reduced tissue accumulation and/or reduced nephrotoxicity observed for these compounds relative to the corresponding compounds that lack the phosphono functionality.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel compounds of the invention, which are derivatives of glycopeptide antibiotics comprising one or more substituents that comprise one or more phosphono groups, as well as to compositions comprising such compounds and to therapeutic methods comprising the administration of such compounds. When describing the compounds, compositions and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

Definitions

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having

from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, n-hexyl, n-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 8 substituents, preferably 1 to 5 substituents, and more preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl, —SO_3H, guanido, and —SO_2-heteroaryl.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, preferably 1–10 carbon atoms, more preferably 1–6 carbon atoms. This term is exemplified by groups such as methylene (—CH_2—), ethylene (—CH_2CH_2—), the propylene isomers (e.g., —$CH_2CH_2CH_2$— and —$CH(CH_3)CH_2$—) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures. Additionally, the term substituted alkylene includes alkylene groups in which from 1 to 5 of the alkylene carbon atoms are replaced with oxygen, sulfur or —NR— where R is hydrogen or alkyl. Examples of substituted alkylenes are chloromethylene (—CH(Cl)—), aminoethylene (—$CH(NH_2)CH_2$—), 2-carboxypropylene isomers (—$CH_2CH(CO_2H)CH_2$—), ethoxyethyl (—CH_2CH_2 O—CH_2CH_2—) and the like.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O—, alkenyl-O—, cycloalkyl-O—, cycloalkenyl-O—, and alkynyl-O—, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O— and include, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O—, substituted alkenyl-O—, substituted cycloalkyl-O—, substituted cycloalkenyl-O—, and substituted alkynyl-O— where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, alkylene-O-substituted alkyl, substituted alkylene-O-alkyl and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy (—CH_2OCH_3), ethylenemethoxy (—$CH_2CH_2OCH_3$), n-propylene-iso-propoxy (—$CH_2CH_2CH_2OCH(CH_3)_2$), methylene-t-butoxy (—CH_2—O—$C(CH_3)_3$) and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy (—CH_2SCH_3), ethylenethiomethoxy (—$CH_2CH_2SCH_3$), n-propylene-iso-thiopropoxy (—$CH_2CH_2CH_2SCH(CH_3)_2$), methylene-t-thiobutoxy (—$CH_2SC(CH_3)_3$) and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1–6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl (—$CH{=}CH_2$), n-propenyl (—$CH_2CH{=}CH_2$), iso-propenyl (—$C(CH_3){=}CH_2$), and the like.

The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1–6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (—CH=CH—), the propenylene isomers (e.g., —$CH_2CH{=}CH$— and —$C(CH_3){=}CH$—) and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl,

heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1–6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (—C≡CH), propargyl (—CH_2C≡CH) and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1–6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (—C≡C—), propargylene (—CH_2C≡C—) and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl.

The term "acyl" refers to the groups HC(O)—, alkyl-C(O)—, substituted alkyl-C(O)—, cycloalkyl-C(O)—, substituted cycloalkyl-C(O)—, cycloalkenyl-C(O)—, substituted cycloalkenyl-C(O)—, aryl-C(O)—, heteroaryl-C(O)— and heterocyclic-C(O)— where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acylamino" or "aminocarbonyl" refers to the group —C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group —NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group —NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O—, substituted alkyl-C(O)O—, cycloalkyl-C(O)O—, substituted cycloalkyl-C(O)O—, aryl-C(O)O—, heteroaryl-C(O)O—, and heterocyclic-C(O)O— wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Preferred aryls include phenyl, naphthyl and the like.

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxy, carboxyalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, sulfonamide, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl, —SO_2-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O— wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group —NH_2.

The term "substituted amino" refers to the group —NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

"Amino acid" refers to any of the naturally occurring amino acids (e.g. Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D, L, or DL form. The side chains of naturally occurring amino acids are well known in the art and include, for example, hydrogen (e.g., as in glycine), alkyl (e.g., as in alanine, valine, leucine, isoleucine, proline), substituted alkyl (e.g., as in threonine, serine, methionine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, and lysine), alkaryl (e.g., as in phenylalanine and tryptophan), substituted arylalkyl (e.g., as in tyrosine), and heteroarylalkyl (e.g., as in histidine).

The term "carboxy" refers to —COOH.

The term "C-terminus" as it relates to a glycopeptide is well understood in the art. For example, for a glycopeptide of formula I, the C-terminus is the position substituted by the group R^3.

The term "dicarboxy-substituted alkyl" refers to an alkyl group substituted with two carboxy groups. This term includes, by way of example, —CH_2(COOH)CH_2COOH and —CH_2(COOH)CH_2CH_2COOH.

The term "carboxyalkyl" or "alkoxycarbonyl" refers to the groups "—C(O)O-alkyl", "—C(O)O-substituted alkyl", "—C(O)O-cycloalkyl", "—C(O)O-substituted cycloalkyl", "—C(O)O-alkenyl", "—C(O)O-substituted alkenyl", "—C(O)O-alkynyl" and "—C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl and —SO_2-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Haloalkyl" refers to alkyl as defined herein substituted by 1–4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3-fluorododecyl, 12,12, 12-trifluorododecyl, 2-bromooctyl, 3-bromo-6-chloroheptyl, and the like.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxy, carboxyalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl, —SO_2-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

"Heteroarylalkyl" refers to (heteroaryl)alkyl- where heteroaryl and alkyl are as defined herein. Representative examples include 2-pyridylmethyl and the like.

The term "heteroaryloxy" refers to the group heteroaryl-O—.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl and the like.

The term "heterocycle" or "heterocyclic" refers to a monoradical saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SO-aryl, —SO-heteroaryl, —SO_2-alkyl, —SO_2-substituted alkyl, —SO_2-aryl, oxo (=O), and —SO_2-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine,

phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

Another class of heterocyclics is known as "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating units of the formula [—$(CH_2$—$)_a$A—] where a is equal to or greater than 2, and A at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only, [—$(CH_2)_3$—NH—]$_3$, [—$((CH_2)_2$—O$)_4$—$((CH_2)_2$—NH$)_2$] and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "heterocyclooxy" refers to the group heterocyclic-O—.

The term "thioheterocyclooxy" refers to the group heterocyclic-S—.

The term "N-terminus" as it relates to a glycopeptide is well understood in the art. For example, for a glycopeptide of formula II, the N-terminus is the position substituted by the group R^{19} and R^{20}.

The term "oxyacylamino" or "aminocarbonyloxy" refers to the group —OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "phosphono" refers to —PO_3H_2.

The term "phosphonomethylamino" refers to —NH—CH_2—P(O)$(OH)_2$.

The term "phosphonomethylaminomethyl" refers to —CH_2—NH—CH_2—P(O)$(OH)_2$.

The term "prodrug" is well understood in the art and includes compounds that are converted to pharmaceutically active compounds of the invention in a mammalian system. For example, see *Remington's Pharmaceutical Sciences,* 1980, vol. 16, Mack Publishing Company, Easton, Pa., 61 and 424.

The term "R-terminus" as it relates to a glycopeptide is well understood in the art. For example, for a glycopeptide of formula I, the R-terminus is the position substituted by the group R^5.

The term "saccharide group" refers to an oxidized, reduced or substituted saccharide monoradical covalently attached to the glycopeptide or other compound via any atom of the saccharide moiety, preferably via the aglycone carbon atom. The term includes amino-containing saccharide groups. Representative saccharide include, by way of illustration, hexoses such as D-glucose, D-mannose, D-xylose, D-galactose, vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, D-glucamine, N-methyl-D-glucamine, D-glucuronic acid, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, sialyic acid, iduronic acid, L-fucose, and the like; pentoses such as D-ribose or D-arabinose; ketoses such as D-ribulose or D-fructose; disaccharides such as 2-O-(α-L-vancosaminyl)-β-D-glucopyranose, 2-O-(3-desmethyl-α-L-vancosaminyl)-β-D-glucopyranose, sucrose, lactose, or maltose; derivatives such as acetals, amines, acylated, sulfated and phosphorylated sugars; oligosaccharides having from 2 to 10 saccharide units. For the purposes of this definition, these saccharide are referenced using conventional three letter nomenclature and the saccharide can be either in their open or preferably in their pyranose form.

The term "amino-containing saccharide group" refers to a saccharide group having an amino substituent. Representative amino-containing saccharide include L-vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, N-methyl-D-glucamine and the like.

The term "spiro-attached cycloalkyl group" refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "stereoisomer" as it relates to a given compound is well understood in the art, and refers another compound having the same molecular formula, wherein the atoms making up the other compound differ in the way they are oriented in space, but wherein the atoms in the other compound are like the atoms in the given compound with respect to which atoms are joined to which other atoms (e.g. an enantiomer, a diastereomer, or a geometric isomer). See for example, *Morrison and Boyde Organic Chemistry,* 1983, 4th ed., Allyn and Bacon, Inc., Boston, Mass., page 123

The term "sulfonamide" refers to a group of the formula —SO_2NRR, where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "thiol" refers to the group —SH.

The term "thioalkoxy" refers to the group —S-alkyl.

The term "substituted thioalkoxy" refers to the group —S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S— wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

The term "thioheteroaryloxy" refers to the group heteroaryl-S— wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "thioether derivatives" when used to refer to the glycopeptide compounds of this invention includes thioethers (—S—), sulfoxides (—SO—) and sulfones (—SO_2—).

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

"Cyclodextrin" includes cyclic molecules containing six or more α-D-glucopyranose units linked at the 1,4 positions by a linkages as in amylose. β-Cyclodextrin or cycloheptaamylose contains seven α-D-glucopyranose units. As used herein, the term "cyclodextrin" also includes cyclodextrin derivatives such as hydroxypropyl and sulfobutyl ether cyclodextrins. Such derivatives are described for example, in U.S. Pat. Nos. 4,727,064 and 5,376,645. One preferred cyclodextrin is hydroxypropyl β-cyclodextrin having a degree of substitution of from about 4.1–5.1 as measured by FTIR. Such a cyclodextrin is available from Cerestar (Hammond, Ind., USA) under the name Cavitron™ 82003.

"Glycopeptide" refers to oligopeptide (e.g. heptapeptide) antibiotics (dalbaheptides), characterized by a multi-ring peptide core optionally substituted with saccharide groups, such as vancomycin. Examples of glycopeptides included in this definition may be found in "Glycopeptides Classification, Occurrence, and Discovery", by Raymond C. Rao and Louise W. Crandall, ("Drugs and the Pharmaceu-

tical Sciences" Volume 63, edited by Ramakrishnan Nagarajan, published by Marcal Dekker, Inc.). Additional examples of glycopeptodes are disclosed in U.S. Pat. Nos. 4,639,433; 4,643,987; 4,497,802; 4,698,327; 5,591,714; 5,840,684; and 5,843,889; in EP 0 802 199; EP 0 801 075; EP 0 667 353; WO 97/28812; WO 97/38702; WO 98/52589; WO 98/52592; and in *J. Amer. Chem. Soc.*, 1996,118, 13107–13108; *J. Amer. Chem. Soc.*, 1997, 119, 12041–12047; and *J. Amer. Chem. Soc.*, 1994, 116, 4573–4590. Representative glycopeptides include those identified as A477, A35512, A40926, A41030, A42867, A47934, A80407, A82846, A83850 ,A84575, AB-65, Actaplanin, Actinoidin, Ardacin, Avoparcin, Azureomycin, Balhimycin, Chloroorientiein, Chloropolysporin, Decaplanin, N-demethylvancomycin, Eremomycin, Galacardin, Helvecardin, Izupeptin, Kibdelin, LL-AM374, Mannopeptin, MM45289, MM47756, MM47761, MM49721, MM47766, MM55260, MM55266, MM55270, MM56597, MM56598, OA-7653, Orenticin, Parvodicin, Ristocetin, Ristomycin, Synmonicin, Teicoplanin, UK-68597, UK-69542, UK-72051, Vancomycin, and the like. The term "glycopeptide" as used herein is also intended to include the general class of peptides disclosed above on which the sugar moiety is absent, i.e. the aglycone series of glycopeptides. For example, removal of the disaccharide moiety appended to the phenol on vancomycin by mild hydrolysis gives vancomycin aglycone. Also within the scope of the invention are glycopeptides that have been further appended with additional saccharide residues, especially aminoglycosides, in a manner similar to vancosamine.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted" means that a group may or may not be substituted with the described substitutent.

As used herein, the terms "inert organic solvent" or "inert solvent" or "inert diluent" mean a solvent or diluent which is essentially inert under the conditions of the reaction in which it is employed as a solvent or diluent. Representative examples of materials which may be used as inert solvents or diluents include, by way of illustration, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ("$CHCl_3$"), methylene chloride (or dichloromethane or "CH_2Cl_2), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The term "nitrogen-linked" or "N-linked" means a group or substituent is attached to the remainder of a compound (e.g. a compound of formula I) through a bond to a nitrogen of the group or substituent. The term "oxygen-linked" means a group or substituent is attached to the remainder of a compound (e.g. a compound of formula I) through a bond to an oxygen of the group or substituent. The term "sulfur-linked" means a group or substituent is attached to the remainder of a compound (e.g. a compound of formula I) through a bond to a sulfur of the group or substituent.

"Pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of the parent compounds and which are not biologically or otherwise harmful as the dosage administered. The compounds of this invention are capable of forming both acid and base salts by virtue of the presence of amino and carboxy groups respectively.

Pharmaceutically acceptable base addition salts may be prepared from inorganic and organic bases. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethyl amine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, and N-ethylpiperidine. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example carboxylic acid amides, including carboxamides, lower alkyl carboxamides, di(lower alkyl) carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The compounds of this invention typically contain one or more chiral centers. Accordingly, this invention is intended to include racemic mixtures, diasteromers, enantiomers and mixture enriched in one or more steroisomer. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers and non-racemic mixtures thereof.

The term "treatment" as used herein includes any treatment of a condition or disease in an animal, particularly a mammal, more particularly a human, and includes:

(i) preventing the disease or condition from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, i.e. arresting its development; relieving the disease or condition, i.e. causing regression of the condition; or. relieving the conditions caused by the disease, i.e. symptoms of the disease.

The term "disease state which is alleviated by treatment with a broad spectrum antibacterial" or "bacterial disease" as used herein is intended to cover all disease states which are generally acknowledged in the art to be usefully treated with a broad spectrum antibacterial in general, and those disease states which have been found to be usefully treated by the specific antibacterials of this invention. Such disease states include, but are not limited to, treatment of a mammal afflicted with pathogenic bacteria, in particular staphylococci (methicillin sensitive and resistant), streptococci (penicillin sensitive and resistant), enterococci (vancomycin sensitive and resistant), and Clostridium difficile.

The term "therapeutically effective amount" refers to that amount which is sufficient to effect treatment, as defined herein, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

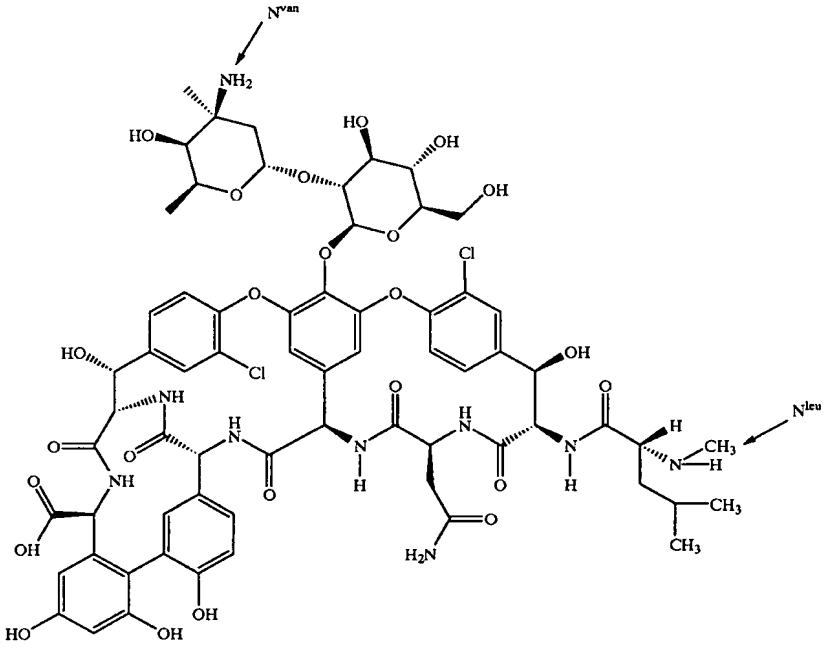
The term "protecting group" or "blocking group" refers to any group which, when bound to one or more hydroxyl,

thiol, amino, carboxy or other groups of the compounds, prevents undesired reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thio, amino, carboxy or other group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product. Protecting groups are disclosed in more detail in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis" 3rd Ed., 1999, John Wiley and Sons, N.Y.

Preferred removable amino blocking groups include conventional substituents such as t-butyoxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), fluorenylmethoxycarbonyl (FMOC), allyloxycarbonyl (ALOC) and the like, which can be removed by conventional conditions compatible with the nature of the product.

Preferred carboxy protecting groups include esters such as methyl, ethyl, propyl, t-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

"Vancomycin" refers to a glycopeptide antibiotic having the formula:



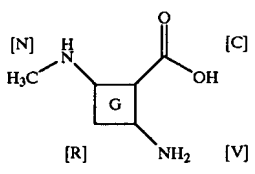
When describing vancomycin derivatives, the term "N^{van}-" indicates that a substituent is covalently attached to the amino group of the vacosamine moiety of vacomycin. Similarly, the term "N^{leu}-" indicates that a substituent is covalently attached to the amino group of the leucine moiety of vancomycin.

General Synthetic Procedures

The glycopeptide compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis,* Third Edition, Wiley, New York, 1999, and references cited therein.

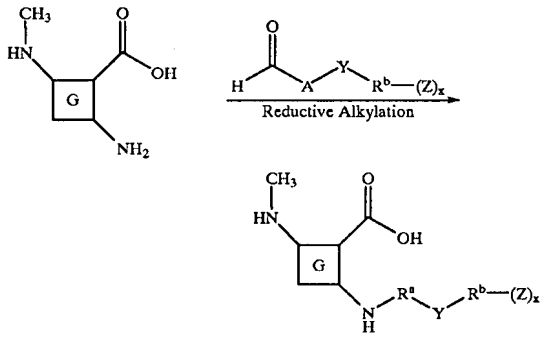
In the following reaction schemes, the glycopeptide compounds are depicted in a simplified form as a box "G" that shows the carboxy terminus labeled [C], the vancosamine amino terminus labeled [V], the "non-saccharide" amino terminus (leucine amine moiety) labeled [N], and optionally, the resorcinol moiety labeled [R] as follows:



A glycopeptide compound of the present invention, which is substituted at the C-terminus with a substituent that comprises one or more (e.g. 1, 2, 3, 4, or 5) phosphono (—PO_3H_2) groups, can be prepared by coupling a corresponding glycopeptide compound wherein the C-terminus is a carboxy group with a suitable phosphono containing compound. For example, a glycopeptide compound wherein the C-terminus is a carboxy group can be coupled with a phosphono containing amine, alcohol, or thiol compound to form an amide, an ester, or a thioester, respectively. For example a glycopeptide compound of formula I wherein R^3 is a nitrogen linked moiety comprising one or more phosphono groups can be prepared by coupling a corresponding glycopeptide compound of formula I wherein R^3 is hydroxy with the requisite phosphono-containing amine to form the formula I wherein R^3 is a nitrogen linked moiety comprising one or more phosphono groups.

A glycopeptide compound of the present invention, which is substituted at the C-terminus with a substituent that comprises one or more (e.g. 1, 2, 3, 4, or 5) phosphono (—PO_3H_2) groups, and wherein the vancosamine amino terminus (V) is substituted, can be prepared by first reductively alkylating the corresponding glycopeptide compound wherein the vancosamine amino terminus (V) is the free amine (NH_2) and then coupling the corresponding glycopeptide compound with the requisite phosphono containing compound (e.g. phosphono containing amine, alcohol, or thiol).

By way of illustration, a glycopeptide compound, such as vancomycin, can first be reductive alkylated as shown in the following reaction:



where A represents R^a minus one carbon atom and R^a, R^b, Y, Z and x are as defined herein. This reaction is typically conducted by first contacting one equivalent of the glycopeptide, i.e., vancomycin, with an excess, preferably from 1.1 to 1.3 equivalents, of the desired aldehyde in the presence of an excess, preferably about 2.0 equivalents, of a tertiary amine, such as diisopropylethylamine (DIPEA) and the like. This reaction is typically conducted in an inert diluent, such as DMF or acetonitrile/water, at ambient temperature for about 0.25 to 2 hours until formation of the corresponding imine and/or hemiaminal is substantially complete. The resulting imine and/or hemiaminal is typically not isolated, but is reacted in situ with a reducing agent, such as sodium cyanoborohydride, pyridine borane, or the like, to afford the corresponding amine. This reaction is preferably conducted by contacting the imine and/or hemiaminal with an excess, preferably about 3 equivalents, of trifluoroacetic acid, followed by about 1 to 1.2 equivalents of the reducing agent at ambient temperature in methanol or acetonitrile/water. The resulting alkylated product is readily purified by conventional procedures, such as precipitation and/or reverse-phase HPLC. Surprisingly, by forming the imine and/or hemiaminal in the presence of a trialkyl amine, and then acidifying with trifluoroacetic acid before contact with the reducing agent, the selectivity for the reductive alkylating reaction is greatly improved, i.e., reductive alkylating at the amino group of the saccharide (e.g., vancosamine) is favored over reductive alkylating at the N-terminus (e.g., the leucinyl group) by at least 10:1, more preferably 20:1.

The above process is a significantly improvement over previous methods for selectively alkylating an amino saccharide group of a glycopeptide antibiotic. Thus, the present invention also provides a method for alkylating a glycopeptide that comprises a saccharide-amine comprising:

combining an aldehyde or ketone, a suitable base, and the glycopeptide, to provide a reaction mixture;

acidifying the reaction mixture; and

combining the reaction mixture with a suitable reducing agent, to provide a glycopeptide that is alkylated at the saccharide-amine. Preferably, the glycopeptide comprises at least one amino group other than the saccharide-amine.

Preferably, the reductive alkylating at the saccharide-amine is favored over reductive alkylating at another amino group of the glycopeptide by at least about 10:1; and more preferably, by at least about 15:1 or about 20:1.

The reductive alkylating process of the invention is typically carried out in the presence of a suitable solvent or combination of solvents, such as, for example, a halogenated hydrocarbon (e.g. methylene chloride), a linear or branched ether (e.g. diethyl ether, tetrahydrofuran), an aromatic hydrocarbon (e.g. benzene or toluene), an alcohol (methanol, ethanol, or isopropanol), dimethylsulfoxide (DMSO), N,N-dimethylformamide, acetonitrile, water, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone, tetramethyl urea, N,N-dimethylacetamide, diethylformamide (DMF), 1-methyl-2-pyrrolidinone, tetramethylenesulfoxide, glycerol, ethyl acetate, isopropyl acetate, N,N-dimethylpropylene urea (DMPU) or dioxane. Preferably the alkylating is carried out in acetonitrile/water, or DMF/methanol.

Preferably the reduction (i.e. treatment with the reducing agent) is carried out in the presence of a protic solvent, such as, for example, an alcohol (e.g. methanol, ethanol, propanol, isopropanol, or butanol), water, or the like.

The reductive alkylating process of the invention can be carried out at any suitable temperature from the freezing point to the reflux temperature of the reaction mixture. Preferably the reaction is carried out at a temperature in the range of about 0° C. to about 100° C. More preferably at a temperature in a range of about 0° C. to about 50° C., or in a range of about 20° C. to about 30° C.

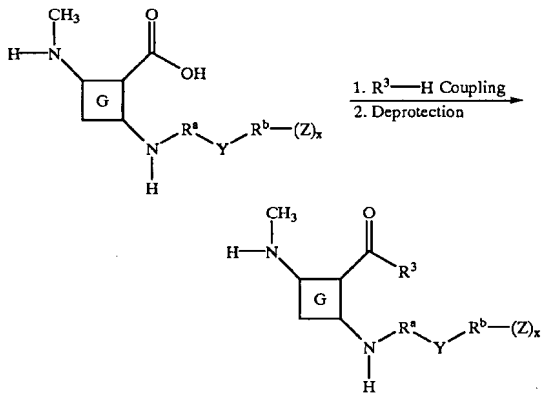
Any suitable base can be employed in the reductive alkylating process of the invention. Suitable bases include tertiary amines (e.g. diisopropylethylamine, N-methylmorpholine or triethylamine) and the like.

Any suitable acid can be used to acidify the reaction mixture. Suitable acids include carboxylic acids (e.g. acetic acid, trichloroacetic acid, citric acid, formic acid, or trifluoroacetic acid), mineral acids (e.g. hydrochloric acid, sulfuric acid, or phosphoric acid), and the like. A preferred acid is trifluoroacetic acid.

Suitable reducing agents for carrying out reductive alkylating process of the invention are known in the art. Any suitable reducing agent can be employed in the methods of the invention, provided it is compatible with the function-

ality present in the glycopeptide. For example, suitable reducing agents include sodium cyanoborohydride, sodium triacetoxyborohydride, pyridine/borane, sodium borohydride, and zinc borohydride. The reduction can also be carried out in the presence of a transition metal catalyst (e.g. palladium or platinum) in the presence of a hydrogen source (e.g. hydrogen gas or cyclohexadiene). See for example, *Advanced Organic Chemistry,* Fourth Edition, John Wiley & Sons, New York (1992), 899–900.

The glycopeptide derivative resulting from the reductive alkylating is then coupled with a phosphono containing amine (R^3—H) to form an amide bond. This reaction is illustrated by the following reaction:



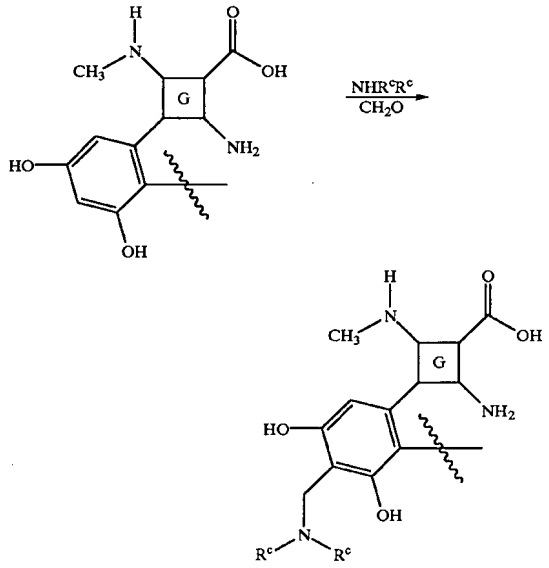
where R^3 is a nitrogen-linked group that comprises one or more phosphono groups. In this reaction, the glycopeptide derivative is typically contacted with the amine in the presence of a peptide coupling reagent, such as PyBOP and HOBT, to provide the amide. This reaction is typically conducted in an inert diluent, such as DMF, at a temperature ranging from about 0° C. to about 60° C. for about 1 to 24 hours or until the coupling reaction is substantially complete. Subsequent deprotection using conventional procedures and reagents affords the compound of this invention.

If desired, the amine coupling step described above can be conducted first to provide an amide, followed by reductive alkylating and deprotection to afford the compound of the invention.

If desired, the glycopeptide compounds of this invention can also be prepared in a step-wise manner in which a precursor to the —R^a—Y—R^b—$(Z)_x$, group is first attached the glycopeptide by reductive alkylating, followed by subsequent elaboration of the attached precursor using conventional reagent and procedures to form the —R^a—Y—R^b—$(Z)_x$, group. Additionally, ketones may also be employed in the above-described reductive alkylating reactions to afford a-substituted amines.

Any glycopeptide having an amino group may be employed in these reductive alkylating reactions. Such glycopeptides are well-known in the art and are either commercially available or may be isolated using conventional procedures. Suitable glycopeptides are disclosed, by way of example, in U.S. Pat. Nos. 3,067,099; 3,338,786; 3,803,306; 3,928,571; 3,952,095; 4,029,769; 4,051,237; 4,064,233; 4,122,168; 4,239,751; 4,303,646; 4,322,343; 4,378,348; 4,497,802; 4,504,467; 4,542,018; 4,547,488; 4,548,925; 4,548,974; 4,552,701; 4,558,008; 4,639,433; 4,643,987; 4,661,470; 4,694,069; 4,698,327; 4,782,042; 4,914,187; 4,935,238; 4,946,941; 4,994,555; 4,996,148; 5,187,082; 5,192,742; 5,312,738; 5,451,570; 5,591,714; 5,721,208; 5,750,509; 5,840,684; and 5,843,889. Preferably, the glycopeptide employed in the above reaction is vancomycin.

As illustrated in the following scheme, a phosphono containing aminoalkyl sidechain at the resorcinol moiety of a glycopeptide, such as vancomycin, can be introduced via a Mannich reaction (in this scheme, the resorcinol moiety of the glycopeptide is illustrated for clarity). In this reaction, an amine of formula NHRR' (wherein one or both of R and R' is a group that comprises one or more phosphono groups), and an aldehyde (e.g. CH_2O), such as formalin (a source of formaldehyde), are reacted with the glycopeptide under basic conditions to give the glycopeptide derivative.



Compounds of the invention comprising a sulfoxide or sulfone can be prepared from the corresponding thio compounds using conventional reagents and procedures. Suitable reagents for oxidizing a thio compound to a sulfoxide include, by way of example, hydrogen peroxide, peracides such as 3-chloroperoxybenzoic acid (MCPBA), sodium periodate, sodium chlorite, sodium hypochlorite, calcium hypochlorite, tert-butyl hypochlorite and the like. Chiral oxidizing reagents, (optically active reagents) may also be employed to provide chiral sulfoxides. Such optically active reagents are well-known in the art and include, for example, the reagents described in Kagen et al., *Synlett.,* 1990, 643–650.

The aldehydes and ketones employed in the above reactive alkylating reactions are also well-known in the art and are either commercially available or can be prepared by conventional procedures using commercially available starting materials and conventional reagents (for example see March, *Advanced Organic Chemistry,* Fourth Edition, John Wiley & Sons, New York (1992), and references cited therein).

The phosphono substituted compounds (e.g. the phosphono substituted amines, alcohols, or thiols) are either commercially available or can be prepared by conventional procedures using commercially available starting materials and reagents. See for example, *Advanced Organic Chemistry,* Jerry March, 4th ed., 1992, John Wiley and Sons, New York, page 959; and Frank R. Hartley (ed.) *The Chemistry of Organophosphorous Compounds,* vol. 1–4, John Wiley and Sons, New York (1996). Aminomethylphos-

phonic acid is commercially available from Aldrich Chemical Company, Milwaukee, Wis.

Additional details and other methods for preparing the compounds of this invention are described in the Examples below.

Pharmaceutical Compositions

This invention also includes pharmaceutical composition containing the novel glycopeptide compounds of this invention. Accordingly, the glycopeptide compound, preferably in the form of a pharmaceutically acceptable salt, can be formulated for oral or parenteral administration for the therapeutic or prophylactic treatment of bacterial infections.

By way of illustration, the glycopeptide compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions will contain from about 0.1 to about 90% by weight of the active compound, and more generally from about 10 to about 30%. The pharmaceutical compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

A liquid composition will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s), for example ethanol, glycerine, sorbitol, non-aqueous solvent such as polyethylene glycol, oils or water, optionally with a suspending agent, a solubilizing agent (such as a cyclodextrin), preservative, surfactant, wetting agent, flavoring or coloring agent. Alternatively, a liquid formulation can be prepared from a reconstitutable powder.

For example a powder containing active compound, suspending agent, sucrose and a sweetener can be reconstituted with water to form a suspension; and a syrup can be prepared from a powder containing active ingredient, sucrose and a sweetener.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid compositions. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, microcrystalline cellulose and binders, for example polyvinylpyrrolidone. The tablet can also be provided with a color film coating, or color included as part of the carrier(s). In addition, active compound can be formulated in a controlled release dosage form as a tablet comprising a hydrophilic or hydrophobic matrix.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, for example by incorporation of active compound and excipients into a hard gelatin capsule. Alternatively, a semi-solid matrix of active compound and high molecular weight polyethylene glycol can be prepared and filled into a hard gelatin capsule; or a solution of active compound in polyethylene glycol or a suspension in edible oil, for example liquid paraffin or fractionated coconut oil can be prepared and filled into a soft gelatin capsule.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. Additionally, it may be desirable to add a coloring agent to make the dosage form more attractive in appearance or to help identify the product.

The compounds of the invention and their pharmaceutically acceptable salts that are active when given parenterally can be formulated for intramuscular, intrathecal, or intravenous administration.

A typical composition for intra-muscular or intrathecal administration will consist of a suspension or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical composition for intravenous or intrathecal administration will consist of a sterile isotonic aqueous solution containing, for example active ingredient and dextrose or sodium chloride, or a mixture of dextrose and sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus dextrose injection, Normosol-M and dextrose, Isolyte E, acylated Ringer's injection, and the like. Optionally, a co-solvent, for example, polyethylene glycol; a chelating agent, for example, ethylenediamine tetracetic acid; a solubilizing agent, for example, a cyclodextrin; and an anti-oxidant, for example, sodium metabisulphite, may be included in the formulation. Alternatively, the solution can be freeze dried and then reconstituted with a suitable solvent just prior to administration.

In a preferred embodiment, the glycopeptide derivatives of this invention are formulated in an aqueous solution containing a cyclodextrin. In another preferred embodiment the glycopeptide derivatives of this invention are formulated as a lyophilized powder containing a cyclodextrin or as a sterile powder containing a cyclodextrin. Preferably, the cyclodextrin is hydroxypropyl-β-cyclodextrin or sulfobutyl ether β-cyclodextrin; more preferably, the cyclodextrin is hydroxypropyl-β-cyclodextrin. Typically, in an injectable solution, the cyclodextrin will comprise about 1 to 25 weight percent; preferably, about 2 to 10 weight percent; more preferable, about 4 to 6 weight percent, of the formulation. Additionally, the weight ratio of the cyclodextrin to the glycopeptide derivative will preferably be from about 1:1 to about 10: 1.

The compounds of the invention and their pharmaceutically acceptable salts which are active on rectal administration can be formulated as suppositories. A typical suppository formulation will generally consist of active ingredient with a binding and/or lubricating agent such as a gelatin or cocoa butter or other low melting vegetable or synthetic wax or fat.

The compounds of this invention and their pharmaceutically acceptable salts which are active on topical administration can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. No. 5,023,252, issued Jun. 11, 1991. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically

effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses are in the general range of from 0.01–100 mg/kg/day, preferably 0.1–50 mg/kg/day. For an average 70 kg human, this would amount to 0.7 mg to 7 g per day, or preferably 7 mg to 3.5 g per day. A more preferred dose for a human is about 500 mg to about 2 g per day.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences,* Mace Publishing Company, Philadelphia, Pa., 17th ed. (1985).

The following illustrate representative pharmaceutical compositions of the present invention.

FORMULATION EXAMPLE A

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	200
Lactose, spray-dried	148
Magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

FORMULATION EXAMPLE B

This example illustrates the preparation of another representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	400
Cornstarch	50
Lactose	145
Magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

FORMULATION EXAMPLE C

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention.

An oral suspension is prepared having the following composition.

Ingredients	
Active Compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.1 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

FORMULATION EXAMPLE D

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

Ingredients	
Active Compound	0.2 g
Sodium Acetate Buffer Solution (0.4 M)	2.0 ml
HCl (1 N)	q.s. to pH 4
Water (distilled, sterile)	q.s. to 20 ml

FORMULATION EXAMPLE E

This example illustrates the preparation of a representative pharmaceutical composition for injection of a compound of this invention.

A reconstituted solution is prepared by adding 20 ml of sterile water to 1 g of the compound of this invention. Before use, the solution is then diluted with 200 ml of an intravenous fluid that is compatible with the active compound. Such fluids are chosen from 5% dextrose solution, 0.9% sodium chloride, or a mixture of 5% dextrose and 0.9% sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, Normosol-M and 5% dextrose, Isolyte E, and acylated Ringer's injection

FORMULATION EXAMPLE F

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation is prepared having the following composition:

Ingredients	
Active Compound	0.1–5.0 g
Hydroxypropyl-β-cyclodextrin	1–25 g
5% Aqueous Dextrose Solution (sterile)	q.s. to 100 ml

The above ingredients are blended and the pH is adjusted to 3.5±0.5 using 0.5 N HCl or 0.5 N NaOH.

FORMULATION EXAMPLE G

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

A frozen solution suitable for injection is prepared having the following composition:

Frozen Solution	
Active Compound	250 mg to 1000 mg
Hydroxypropyl-β-cyclodextrin	250 mg to 10 g
Excipients-e.g., dextrose	0–50 g
Water for Injection	10–100 ml

The weight ratio of hydroxypropyl-β-cyclodextrin to the active compound will typically be from about 1:1 to about 10:1.

The weight ratio of hudroxypropyl-β-cyclodextrin to the active compound will typically be from about 1:1 to about 10:1.

Representative Procedure: Hydroxypropyl-β-cyclodextrin and excipients, if any, are dissolved in about 80% of the water for injection and the active compound is added and dissolved. The pH is adjusted with 1 M sodium hydroxide to 4.7±0.3 and the volume is then adjusted to 95% of the final volume with water for injection. The pH is checked and adjusted, if necessary, and the volume is adjusted to the final volume with water for injection. The formulation is then sterile filtered through a 0.22 micron filter and placed into a sterile vial under aseptic conditions. The vial is capped, labeled and stored frozen.

FORMULATION EXAMPLE H

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

A lyophilized powder useful for preparing an injectable solution is prepared having the following composition:

Lyophilized Powder	
Active Compound	250 mg to 1000 mg
Hydroxypropyl-β-cyclodextrin	250 mg to 10 g
Excipients-e.g., mannitol, sucrose and/or lactose	0–50 g
Buffer agent-e.g., citrate	0–500 mg

The weight ratio of hydroxypropyl-β-cyclodextrin to the active compound will typically be from about 1:1 to about 10:1.

Representative Procedure: Hydroxypropyl-β-cyclodextrin and excipients and/or buffering agents, if any, are dissolved in about 60% of the water for injection. The active compound is added and dissolved and the pH is adjusted with 1 M sodium hydroxide to 4.0–5.0 and the volume is adjusted to 95% of the final volume with water for injection. The pH is checked and adjusted, if necessary, and the volume is adjusted to the final volume with water for injection. The formulation is then sterile filtered through a 0.22 micron filter and placed into a sterile vial under aseptic conditions. The formulation is then freeze-dried using an appropriate lyophilization cycle. The vial is capped (optionally under partial vacuum or dry nitrogen), labeled and stored at room temperature or under refrigeration.

FORMULATION EXAMPLE I

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

A sterile powder useful for preparing an injectable solution is prepared having the following composition:

Sterile Powder	
Active Compound	250 mg to 1000 mg
Hydroxypropyl-β-cyclodextrin	250 mg to 10 g[1]
Excipients	optional

The weight ratio of hydroxypropyl-β-cyclodextrin to the active will typically be from about 1:1 to about 10:1.

Representative Procedure: Hydroxypropyl-β-cyclodextrin and the active compound (and any excipients) are dispersed into an appropriate sterile container and the container is sealed (optionally under partial vacuum or dry nitrogen), labeled and stored at room temperature or under refrigeration.

Administration of Representative Formulations H and I to a Patient

The pharmaceutical formulations described in formulation examples H and I above can be administered intravenously to a patient by the appropriate medical personnel to treat or prevent gram-positive infections. For administration, the above formulations can be reconstituted and/or diluted with a diluent, such as 5% dextrose or sterile saline, as follows:

Representative Procedure: The lyophilized powder of formulation example H (e.g., containing 1000 mg of active compound) is reconstituted with 20 ml of sterile water and the resulting solution is further diluted with 80 ml of sterile saline in a 100 ml infusion bag. The diluted solution is then administered to the patient intravenously over 30 to 120 minutes.

FORMULATION EXAMPLE J

This example illustrates the preparation of a representative pharmaceutical composition for topical application of a compound of this invention.

Ingredients	grams
Active compound	0.2–10
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60° C. with stirring. A sufficient quantity of water at 60° C. is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

FORMULATION EXAMPLE K

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

A suppository totaling 2.5 grams is prepared having the following composition:

Ingredients	
Active Compound	500 mg
Witepsol H-15*	balance

(*triglycerides of saturated vegetable fatty acid; a product of Riches-Nelson, Inc., New York, N.Y.)

A preferred active compound for incorporation in Formulations A–K is compound 11, or a pharmaceutically acceptable salt thereof (e.g. the hydrochloride salt).

Utility

The glycopeptide compounds of this invention, and their pharmaceutically acceptable salts, are useful in medical treatments and exhibit biological activity, including antibacterial activity, which can be demonstrated in using the tests described herein. Such tests are well known to those skilled in the art, and are referenced and described in Lorian "Antibiotics in Laboratory Medicine", Fourth Edition, Williams and Wilkins (1991).

Accordingly, this invention provides methods for treating bacterial or infectious diseases, especially those caused by Gram-positive microorganisms, in animals. The compounds of this invention are particularly useful in treating infections caused by methicillin-resistant staphylococci. Also, the compounds are useful in treating infection due to enterococci, including vancomycin-resistant enterococci (VRE). Examples of such diseases include severe staphylococcal infections, such as staphylococcal endocarditis and staphylococcal septicemia. The animal treated may be either susceptible to, or infected with, the microorganism. The method of treatment typically comprises administering to the animal an amount of a compound of this invention which is effective for this purpose.

In practicing this method, the antibiotic can be administered in a single daily dose or in multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several days or for from one to six weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms in the infection. Preferably, the compounds of the invention are administered intervenously.

Among other properties, the glycopeptide compounds of the invention have been found to have reduced mammalian toxicity when administered to a mammal. For example, the phosphono substituted derivatives of the invention have been found to have reduced liver and/or kidney accumulation compared to the corresponding non-phosphono substituted compounds. Moreover, certain compounds of this invention are expected to have reduced nephrotoxicity. Additionally, it has been discovered that the addition of a cyclodextrin compound to a pharmaceutical composition containing the glycopeptide compounds of this invention further reduces the nephrotoxicity and/or tissue accumulation of the glycopeptide compound when administered to a mammal.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. Any abbreviations not defined have their generally accepted meaning. Unless otherwise stated, all temperatures are in degrees Celsius.

ACN =	acetonitrile
BOC, Boc =	tert-butoxycarbonyl
DIBAL-H =	diisobutylaluminum hydride
DIPEA =	diisopropylethylamine
DMF =	N,N-dimethylformamide
DMSO =	dimethyl sulfoxide
eq. =	equivalent
EtOAc =	ethyl acetate
Fmoc =	9-fluorenylmethoxycarbonyl
HOBT =	1-hydroxybenzotriazole hydrate
Me =	methyl
MS =	mass spectroscopy
PyBOP =	benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
TEMPO =	2,2,6,6-tetramethyl-piperidinyloxy, free radical
TFA =	trifluoroacetic acid
THF =	tetrahydrofuran
TLC, tlc =	thin layer chromatography

In the following examples, vancomycin hydrochloride semi-hydrate was purchased from Alpharma, Inc. Fort Lee, N.J. 07024 (Alpharma AS, Oslo Norway). Other reagents and reactants are available from Aldrich Chemical Co., Milwaukee, Wis. 53201.

General Procedure A

Reductive Alkylating of Vancomycin

To a mixture of vancomycin (1 eq.) and the desired aldehyde (1.3 eq.) in DMF was added DIPEA (2 eq.). The reaction was stirred at ambient temperature for 1–2 hours and monitored by reverse-phase HPLC. Methanol and $NaCNBH_3$ (1 eq.) were added to the solution, followed by TFA (3 eq.). Stirring was continued for an additional hour at ambient temperature. After the reaction was complete, the methanol was removed in vacuo. The residue was precipitated in acetonitrile. Filtration gave the crude product which was then purified by reverse-phase HPLC. If desired, other glycopeptides antibiotics may be used in this procedure.

General Procedure B

Synthesis of 2-(Decylthio)acetaldehyde

Under nitrogen, to a suspension of potassium carbonate (27 g, 200 mmol) in acetone (100 ml) was added decyl bromide (10 ml, 50 mmol) and mercaptoethanol (4.4 ml, 63 mmol). The suspension was stirred at room temperature for 2 days, then partitioned between water and 80% hexane/ethyl acetate. The organic phase was washed with 2N sodium hydroxide, dried over magnesium sulfate, and the volatiles removed under vacuum to give 2-(decylthio) ethanol (10.2 g, 47 mmol) as a colorless liquid that was used without further purification.

Under nitrogen, 2-(decylthio)ethanol (50 g, 230 mmol), N,N-diisopropylethylamine (128 ml, 730 mmol) and methylene chloride (400 ml) were cooled to –40° C. To this solution was added, over 15 minutes, a solution of sulfur trioxide pyridine complex (116 g, 730 mmol) in dimethyl sulfoxide (600 ml) and methylene chloride (200 ml). After addition, the mixture was stirred a further 15 minutes at –40° C., then 600 ml ice water as added. The mixture was removed from the cooling bath, 1 L water was added, and the liquids partitioned. The organic phase was washed with 1 L of 1 N hydrochloric acid, and dried over magnesium sulfate. Filtration gave 600 ml liquid, which was diluted with 600 ml

hexane and passed through 200 ml silica. The silica was washed with 100 ml 50% methylene chloride/hexane, then 300 ml methylene chloride. The combined organics were concentrated in vacuo to give 2-(decylthio)acetaldehyde (48 g, 220 mmol) as a colorless liquid that was used without further purification.

General Procedure C

Synthesis of N^{van}-2-(Decylthio)ethyl Vancomycin

Procedure A: Under nitrogen, vancomycin hydrochloride hydrate (1 g, 0.64 mmol) was added to 2-(decylthio) acetaldehyde (139 mg, 0.64 mmol) in N,N-dimethylformamide (8 ml). N,N-diisopropylethylamine (336 uL, 1.9 mmol) was added and the suspension stirred vigorously for 2.5 hours, over the course of which all the vancomycin dissolved. Solid sodium cyanoborohydride (60 mg, 0.96 mmol) was added, followed by methanol (5 ml) and trifluoroacetic acid (250 uL, 3.2 mmol). The reaction was stirred for 55 minutes at room temperature and analyzed by reverse phase HPLC. The product distribution based on uv absorption at 280nm was as follows:

Elution time (min)	Area %	Product
2.0	29	vancomycin
3.1	50	N^{van}-2-(decylthio)ethyl vancomycin
3.2	2	—
3.3	7	N^{leu}-2-(decylthio)ethyl vancomycin
3.9	13	N^{van}, N^{leu}-bis-[2-(decylthio)ethyl]vancomycin
4.0	0.5	—

Procedure B: Under nitrogen, to a solution of 2-(decylthio)acetaldehyde (crude, 48 g, 220 mmol) in N,N-dimethylformamide (1.4 L) was added solid vancomycin hydrochloride hydrate (173 g, 110 mmol) followed by N,N-diisopropylethylamine (58 ml, 330 mmol). The suspension was stirred vigorously at room temperature for 2 hours, in the course of which time all the vancomycin fully dissolved, then trifluoroacetic acid (53 ml, 690 mmol) was added. The solution was stirred a further 90 minutes, then solid sodium cyanoborohydride (10.5 g, 170 mmol) followed by methanol (800 ml) were added. After three hours the reaction was analyzed by reverse-phase HPLC. The product distribution based on uv absorption at 280nm was as follows:

Elution time (min)	Area %	Product
2.0	15	vancomycin
3.2	77	N^{van}-2-(decylthio)ethyl vancomycin
3.3	3	—
3.4	0.5	N^{leu}-2-(decylthio)ethyl vancomycin
4.0	0.8	N^{van},N^{leu}-bis-[2-(decylthio)ethyl]vancomycin
4.1	4	—

The reaction mixture from either of the above procedures was poured into water (7 L), resulting in a slightly cloudy solution. The pH of the solution was adjusted to 5 with saturated sodium bicarbonate, resulting in the formation of a white precipitate. This precipitate was collected by filtration, washed with water then ethyl acetate and dried under vacuum to afford N^{van}-2-(decylthio)ethyl vancomycin, which was used without further purification.

Procedure C: A solution of vancomycin hydrochloride (3.0 g, 2.1 mmol) in ACN/H_2O (1:1, 30 ml) was treated with diisopropylethylamine (0.54 g, 0.72 ml, 4.2 mmol) followed by 2-(decylthio)acetaldehyde (0.91 g, 4.2 mmol) at 25° C. After 30 min, the reaction mixture was treated with TFA (1.92 g, 1.29 ml, 16.8 mmol) followed by $NaCNBH_3$ (0.132 g, 2.1 mmol). After 5 to 10 minutes, the crude product N^{van}-2-(decylthio)ethyl vancomycin is precipitated in acetonitrile (300 ml).

Example 1

Preparation of Compound 3

(Formula II wherein R^3 is N-(phosphonomethyl)-amino; R^5 is Hydrogen; R^{19} is Hydrogen, and R^{20} is —CH_2CH_2—S—$(CH_2)_9CH_3$)

N^{VAN}-(2-decylthio)ethyl vancomycin bistrifluoroacetate (1 g, 0.53 mmol) and diisopropylethylamine (0.23 ml, 1.33 mmol) were combined in DMF (10 ml) and stirred until homogeneous. HOBt (0.080 g, 0.58 mmol) and PYBOP (0.300 g, 0.58 mmol) were then added to the reaction mixture. After 5–10 minutes a homogeneous solution containing (aminomethyl)phosphonic acid (0.060 g, 0.53 mmol) and diisopropylethylamine (0.23 ml, 1.33 mmol) in water (3 ml) was added. The reaction was stirred at room temperature and monitored by MS. When the reaction was judged to be complete, the reaction mixture was diluted with acetonitrile (40 ml) and centrifuged. The supernatant was discarded and the remaining pellet containing desired product was dissolved in 50% aqueous acetonitrile (10 ml) and purified by reverse phase preparative HPLC to give the title compound. MS calculated (M+) 1742.7; found (MH+) 1743.6.

Example 2

Preparation of Compound 11

(Formula II wherein R^3 is —OH; R^5 N-(phosphonomethyl)-aminomethyl; R^{19} is Hydrogen, and R^{20} is —CH_2CH_2—NH—$(CH_2)_9CH_3$)

(Aminomethyl)phosphonic acid (3.88 g, 35 mmol) and diisopropylethylamine (6.1 ml, 35 mmol) were combined in water (40 ml) and stirred until homogeneous. Acetonitrile (50 ml) and formaldehyde (37% solution in H_2O; 0.42 ml, 05.6 mmol) were then added to the reaction mixture. After approximately 15 minutes both N^{VAN}-decylaminoethyl vancomycin tristrifluoroacetate (10.0 g, 5.1 mmol) and diisopropylethylamine (6.1 ml, 35 mmol) were added to the reaction mixture. The reaction was stirred at room temperature for approximately 18 hrs, at which time the pH was adjusted to about 7 with 20% TFA, acetonitrile was removed in vacuo, and the residue was lyophylized. The resulting solid was triturated with water (100 mL), collected by filtration, dried in vacuo and purified by reverse phase preparative HPLC to give the title compound. MS calculated (MH+) 1756.6; found (MH+) 1756.6.

Compound 11 was also prepared as follows.

The quinuclidine salt of N^{VAN}-(decylaminoethyl) vancomycin (500 mg, 0.28 mmol, sub-part f below) and aminomethylphosphonic acid (155 mg, 1.4 mmol) were slurried in 50% aqueous acetonitrile (10 mL). Diisopropylethylamine (972 uL, 720 mg, 5.6 mmol) was added and the mixture stirred at room temperature until the solids had dissolved. The reaction mixture was then cooled in an ice bath and formalin (3.7%, made by diluting commercial 37%

formalin 1:9 with 50% ACN/water, 220 uL, 8.8 mg, 0.29 mmol) was added. The reaction mixture was stirred at 0° for 15 hours, at which time the reaction to be complete. The reaction was quenched at 0° by adding 3N HCl to about pH 2. The mixture was diluted to 50 mL with 50% ACN/water, and then acetonitrile was added (75 mL, followed by 5x10 mL at 5 minute intervals ,125 mL total) to precipitate the product. The solid was collected by vacuum filtration and dried in vacuo. Purification by reverse phase preparative HPLC gave the title compound.

The intermediate N^{VAN}-decylaminoethyl vancomycin tris-trifluoroacetate was prepared as follows.

a. N-Fmoc-2-(decylamino)ethanol. 2-(n-Decylamino) ethanol (2.3 g, 11 mmol, 1.1 eq) and DIPEA (2.0 ml, 11 mmol, 1.1 eq) were dissolved in methylene chloride (15 ml) and cooled in an ice bath. 9-Fluorenylmethyl chloroformate (2.6 g, 10 mmol, 1.0 eq) in methylene chloride (15 ml) was added, the mixture stirred for 30 minutes then washed with 3N hydrochloric acid (50 ml) twice and saturated sodium bicarbonate (50 ml). The organics were dried over magnesium sulfate, and the solvents removed under reduced pressure. N-Fmoc-2-(decylamino)ethanol (4.6 g, 11 mmol, 108%) was used without further purification.

b. N-Fmoc-decylaminoacetaldehyde. To a solution of oxalyl chloride (12.24 ml) and methylene chloride (50 mL) at −35 to −45° C. was added DMSO (14.75 g) in methylene chloride (25 mL) over 20 minutes. The reaction mixture was stirred for 10 minutes at −35 to −45° C. A solution of N-Fmoc-decylaminoethanol (20.0 g) in methylene chloride (70 mL) was added over 25 minutes and then stirred 40 minutes at −35 to −45° C. Triethylamine (21.49 g) was then added and the mixture stirred for 30 minutes at −10 to −20° C. The reaction mixture was quenched with water (120 mL) followed by concentrated sulfuric acid (20.0 g) while maintaining the internal temperature at 0–5° C. The organic layer was isolated and washed with 2% sulfuric acid (100 mL) followed by water (2x100 mL). The organic solution was distilled under vacuum at 60° C. to about 100 mL. Heptane (100 mL) was added, the temperature of the oil bath raised to 80° C. and the distillation was continued until the residual volume was 100 mL. More heptane (100 mL) was added and the distillation repeated to a volume of 100 mL. The heating bath was replaced with a cold water bath at 15° C. The bath was cooled slowly to 5° C. over 20 minutes to start the precipitation of the product. The slurry was then cooled to −5 to −10° C. and the slurry was stirred for 2 hours. The solid was then collected on a Buchner funnel and washed with cold (−5° C.) heptane (2x15 mL). The wet solid was dried in vacuo to yield the aldehyde.

c. N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin trifluoroacetate. Vancomycin hydrochloride (12 g, 7.7 mmol, 1.0 eq), N-Fmoc-2-(n-decylamino)-acetaldehyde (3.2 g, 7.6 mmol, 1.0 eq) and DIPEA (2.6 ml, 14.9 mmol, 2.0 eq) were stirred at room temperature in DMF (120 ml) for 90 minutes. Sodium cyanoborohydride (1.4 g, 22 mmol, 3.0 eq) was added, followed by methanol (120 ml) then trifluoroacetic acid (1.8 ml, 23 mmol, 3.0 eq). The mixture was stirred for 60 minutes at room temperature, then the methanol removed under reduced pressure. The resulting solution was added to 600 ml diethyl ether giving a precipitate which was filtered, washed with ether, and dried under vacuum. The crude product was purified on a reverse-phase flash column, eluting with 10, 20, 30% acetonitrile in water (containing 0.1% trifluoroacetic acid) to remove polar impurities (such as residual vancomycin) then the product was eluted with 70% acetonitrile in water (containing 0. 1% trifluoroacetic acid) to give 9 g of N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin as its trifluoroacetate salt (4.3 mmol, 56%).

d. N^{van-2}-(n-Decylamino)ethyl vancomycin trifluoroacetate. N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin (100 mg) was dissolved in 1 ml DMF (1 ml) and treated with piperidine (200 uL) for 30 minutes. The mixture was precipitated into ether, centrifuged and washed with acetonitrile. Reverse-phase preparative HPLC (10–70% acetonitrile in water containing 0.1% trifluoroacetic acid over 120 minutes) gave N^{van}-2-(n-decylamino)ethyl vancomycin as its TFA salt.

The intermediate quinuclidine salt of N^{VAN}-decylaminoethyl vancomycin was prepared as follows.

e. N^{van}-(N'-Fmoc-decylaminoethyl) vancomycin. To a 2 L flask equipped with a mechanical stirrer was added vancomycin hydrochloride (50.0 g), N-Fmoc-decylaminoacetaldehyde (13.5 g), DMF (400 mL) and N,N-diisopropylethylamine (11.7 mL). The suspension was stirred at room temperature for 2 hours, at which time the solids had dissolved. Methanol (190 mL) followed by trifluoroacetic acid (10.4 mL) was added. After the reaction mixture had stirred for 5 minutes, borane-pyridine complex (3.33 g) was added in one portion, and rinsed in with methanol (10 mL). After stirring 4 hours, the reaction was cooled to 5–10° C. with an ice bath and water (675 mL) was added at a rate to keep the temperature below 20° C. The reaction mixture was warmed to room temperature and 10% NaOH was added to pH 4.2–4.3 (approx 15 mL). The resultant slurry was cooled in an ice bath for 1 hour, and then the product is collected by vacuum filtration and washed with cold water (2x100 mL). The wet solid was dried in vacuo at 50° C. to give the title compound as an off-white to pale-pink solid.

f. N^{VAN}-(decylaminoethyl) vancomycin quinuclidine salt. N^{van}-(N'-Fmoc-decylaminoethyl) vancomycin (88 g, 42 mmol) was dissolved in DMF (500 mL) by stirring at room temperature for 1 hour. Quinuclidine (9.4 g, 84 mmol) was added, and the reaction mixture stirred for 18 hours. The DMF was removed in vacuo and the solid was triturated with acetonitrile (700 mL) for 3 hours. The solid was collected on a Buchner funnel and triturated with acetonitrile (200 mL) for 16 hours. More acetonitrile (700 mL) was added at this time, and the solid was collected on a Buchner funnel, washed with acetonitrile (500 mL), and then resuspended in acetonitrile (500 mL). After stirring for 2 hours, the solid was collected on a Buchner funnel and dried in vacuo to give the title compound.

Example 3

Preparation of Compound 12

(Formula II wherein R^3 is —OH; R^5 N-(phosphonomethyl)-aminomethyl; R^{19} is Hydrogen, and R^{20} is $—CH_2CH_2—S—(CH_2)_9CH_3$)

(Aminomethyl)phosphonic acid (0.295 g, 266 mmol) and diisopropylethylamine (0.649 ml, 3.72 mmol) were combined in water (5 ml) and stirred until homogeneous. Formaldehyde (37% solution in H_2O; 0.044 ml, 0.585 mmol) and acetonitrile (5 ml) were then added to the reaction mixture. After approximately 15 minutes both NVAN (2-decylthio) ethyl vancomycin bistrifluoroacetate (1 g, 0.53 mmol) and diisopropylethylamine (0.649 ml, 3.72 mmol) were added to the reaction mixture. The reaction was stirred at room temperature for approximately 18 hrs, at which time the

reaction mixture was diluted with ACN (40 ml) and centrifuged. The supernatant was discarded and the remaining pellet containing desired product was dissolved in 50% aqueous acetonitrile (10 ml) and purified by reverse phase preparative HPLC to give the title compound. MS calculated (M+) 1772.7; found (MH+) 1773.4.

Using the above procedures and the appropriate starting materials the compounds shown in Table I were prepared. The mass spectral data for these compounds were as follows:

Compound No.	MW (freebase)	Observed MH^+
1	1725.63	1726.6
2	1726.62	1727.5
3	1742.68	1743.6
4	1724.64	1725.6
5	1742.96	1743.6
6	1786.03	1786.4
7	1785.04	1785.8
8	1799.07	1799.7
9	1770.74	1771.8
10	1772.99	1774.3
11	1755.66	1756.6
12	1772.71	1773.4
13	1756.64	1757.6
14	1754.67	1755.7
15	1772.99	1773.7
16	1816.06	1816.5
17	1815.01	1816.2
18	1829.10	1829.8
19	1878.1	1878.2
20	1802.74	1803.5
21	1830.75	1831.7
22	1849.66	1850.6
23	1800.76	1801.6
24	1801.04	1801.6
25	1932.86	1934.0
26	1880.12	1880.7

Example 4

Preparation of an Intermediate Useful for Preparing a Compound of the Invention

(Formula II wherein R^3 is —OH; R^5 is H; R^{19} is Hydrogen, and R^{20} is 4-(4-chlorophenyl)benzyl

A three liter 3-necked flask was fitted with a condenser, nitrogen inlet and overhead mechanical stirring apparatus. The flask was charged with pulverized A82846B acetate salt (20.0 g, 1.21×10^{-5} mol) and methanol (1000 ml) under a nitrogen atmosphere, 4'-chlorobiphenylcarboxaldehyde (2.88 g, 1.33×10^{-2} mol, 1.1 eq.) was added to this stirred mixture, followed by methanol (500 ml). Finally, sodium cyanoborohydride (0.84 g, 1.33×10^{-2} mol, 1.1 eq.) was added followed by methanol (500 ml). The resulting mixture was heated to reflux (about 65° C.).

After 1 hour at reflux, the reaction mixture attained homogeneity. After 25 hours at reflux, the heat source was removed and the clear reaction mixture was measured with a pH meter (6.97 at 58.0° C.). 1N NaOH (22.8 ml) was added dropwise to adjust the pH to 9.0 (at 54.7° C.). The flask was equipped with a distillation head and the mixture was concentrated under partial vacuum to a weight of 322.3 grams while maintaining the pot temperature between 40°–45° C.

The distillation head was replaced with an addition funnel containing 500 ml of isopropanol (IPA). The IPA was added dropwise to the room temperature solution over 1 hour. After approximately ⅓ of the IPA was added, a granular precipitate formed. The remaining IPA was added at a faster rate after precipitation had commenced. The flask was weighed and found to hold 714.4 grams of the IPA/methanol slurry.

The flask was re-equipped with a still-head and distilled under partial vacuum to remove the remaining methanol. The resulting slurry (377.8 g) was allowed to chill in the freezer overnight. The crude product was filtered through a polypropylene pad and rinsed twice with 25 ml of cold IPA. After pulling dry on the funnel for 5 minutes, the material was placed in the vacuum oven to dry ta 40° C. A light pink solid (22.87 g (theory=22.43 g)) was recovered. HPLC analysis versus a standard indicated 68.0% weight percent of the title compound (4-[4-chlorophenyl]benzyl-A82846B] in the crude solid, which translated into a corrected crude yield of 69.3%.

The products of the reaction were analyzed by reverse-phase HPLC utilizing a Zorbax SB-C_{18} column with ultraviolet light (UV; 230 nm) detection. A 20 minute gradient solvent system consisting of 95% aqueous buffer/5% CH_3CN at time=0 minutes to 40% aqueous buffer/60% CH_3CN at time=30 minutes was used, where the aqueous buffer was TEAP (5 ml CH_3CN, 3 ml phosphoric acid in 1000 ml water).

The intermediate A82846B acetate salt can be prepared as described in U.S. Pat. No. 5,840,684.

Using procedures described hereinabove, the product of Example 4 can be converted to a compound of the invention wherein R^3 and/or R^5 is a substituent that comprises one or more phosphono groups.

Example 5

Determination of Antibacterial Activity

A. In Vitro Determination of Antibacterial Activity

1. Determination of Minimal Inhibitory Concentrations (MICs)

Bacterial strains were obtained from either American Type Tissue Culture Collection (ATCC), Stanford University Hospital (SU), Kaiser Permanente Regional Laboratory in Berkeley (KPB), Massachusetts General Hospital (MGH), the Centers for Disease Control (CDC), the San Francisco Veterans' Administration Hospital (SFVA) or the University of California San Francisco Hospital (UCSF). Vancomycin resistant enterococci were phenotyped as Van A or Van B based on their sensitivity to teicoplanin. Some vancomycin resistant enterococci that had been genotyped as Van A, Van B, Van C1 or Van C2 were obtained from the Mayo Clinic.

Minimal inhibitory concentrations (MICs) were measured in a microdilution broth procedure under NCCLS guidelines. Routinely, the compounds were serially diluted into Mueller-Hinton broth in 96-well microtiter plates. Overnight cultures of bacterial strains were diluted based on absorbance at 600 nm so that the final concentration in each well was 5×10^5 cfu/ml. Plates were returned to a 35° C. incubator. The following day (or 24 hours in the case of Enterococci strains), MICs were determined by visual inspection of the plates. Strains routinely tested in the initial screen included methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus,* methicillin-sensitive *Staphylococcus epidermidis* (MSSE), methicillin-resistant *Staphylococcus epidermidis* (MSSE), vancomycin sensitive *Enterococcus faecium* (VSE Fm), vancomycin sensitive *Enterococcus faecalis* (VSE Fs), vancomycin resistant *Enterococcus faecium* also resistant to

teicoplanin (VRE Fm Van A), vancomycin resistant *Enterococcus faecium* sensitive to teicoplanin (VRE Fm Van B), vancomycin resistant *Enterococcus faecalis* also resistant to teicoplanin (VRE Fs Van A), vancomycin resistant *Enterococcus faecalis* sensitive to teicoplanin (VRE Fs Van B), enterococcus gallinarium of the Van A genotype (VRE Gm Van A), enterococcus gallinarium of the Van C-1 genotype (VRE Gm Van C-1), enterococcus casseliflavus of the Van C-2 genotype (VRE Cs Van C-2), enterococcus flavescens of the Van C-2 genotype (VRE Fv Van C-2), and penicillin-sensitive Streptococcus pneumoniae (PSSP) and penicillin-resistant Streptococcus pneumoniae (PSRP). Because of the inability of PSSP and PSRP to grow well in Mueller-Hinton broth, MICs with those strains were determined using either TSA broth supplemented with defibrinated blood or blood agar plates. Compounds which had significant activity against the strains mentioned above were then tested for MIC values in a larger panel of clinical isolates including the species listed above as well as non-speciated coagulase negative Staphylococcus both sensitive and resistant to methicillin (MS-CNS and MR-CNS). In addition, they were tested for MICs against gram negative organisms, such as *Escherichia coli* and *Pseudomonas aeruginosa.*

2. Determination of Kill Time

Experiments to determine the time required to kill the bacteria were conducted as described in Lorian, "Antibiotics in Laboratory Medicine", Fourth Edition, Williams and Wilkins (1991). These experiments were conducted normally with both staphylococcus and enterococcus strains.

Briefly, several colonies were selected from an agar plate and grown at 35° C. under constant agitation until it achieved a turbidity of approximately 1.5 and 10^8 CFU/ml. The sample was then diluted to about 6×10^6 CFU/ml and incubated at 35° C. under constant agitation was continued. At various times aliquots were removed and five ten-fold serial dilutions were performed. The pour plate method was used to determine the number of colony forming units (CFUs).

In general, the compounds of the invention were active in the above tests in vitro tests and demonstrated a broad spectrum of activity.

B. In Vivo Determination of Antibacterial Activity

1. Acute Tolerability Studies in Mice

In these studies, a compound of this invention was administered either intravenously or subcutaneously and observed for 5–15 minutes. If there were no adverse effects, the dose was increased in a second group of mice. This dose incrementation continued until mortality occurred, or the dose was maximized. Generally, dosing began at 20 mg/kg and increased by 20 mg/kg each time until the maximum tolerated dose (MTD) is achieved.

2. Bioavailability Studies in Mice

Mice were administered a compound of this invention either intravenously or subcutaneously at a therapeutic dose (in general, approximately 50 mg/kg). Groups of animals were placed in metabolic cages so that urine and feces could be collected for analysis. Groups of animals (n=3) were sacrificed at various times (10 min, 1 hour and 4 hours). Blood was collected by cardiac puncture and the following organs were harvested—lung, liver, heart, brain, kidney, and spleen. Tissues were weighed and prepared for HPLC analysis. HPLC analysis on the tissue homogenates and fluids was used to determine the concentration of the test compound or Iil present. Metabolic products resulting from changes to the test compound were also determined at this juncture.

3. Mouse Septicemia Model

In this model, an appropriately virulent strain of bacteria (most commonly *S. aureus,* or *E. Faecalis* or *E. Faecium*) was administered to mice (N=5 to 10 mice per group) intraperitoneally. The bacteria was combined with hog gastric mucin to enhance virulence. The dose of bacteria (normally 10^5–10^7) was that sufficient to induce mortality in all of the mice over a three day period. One hour after the bacteria was administered, a compound of this invention was administered in a single dose either IV or subcutaneously. Each dose was administered to groups of 5 to 10 mice, at doses that typically ranged from a maximum of about 20 mg/kg to a minimum of less than 1 mg/kg. A positive control (normally vancomycin with vancomycin sensitive strains) was administered in each experiment. The dose at which approximately 50% of the animals are saved was calculated from the results.

4. Neutropenic Thigh Model

In this model, antibacterial activity of a compound of this invention was evaluated against an appropriately virulent strain of bacteria (most commonly S. aureus, or E. Faecalis or E. Faecium, sensitive or resistant to vancomycin). Mice were initially rendered neutropenic by administration of cyclophosphamide at 200 mg/kg on day 0 and day 2. On day 4 they were infected in the left anterior thigh by an IM injection of a single dose of bacteria. The mice were then administered the test compound one hour after the bacteria and at various later times (normally 1, 2.5, 4 and 24 hours) the mice were sacrificed (3 per time point) and the thigh excised, homogenized and the number of CFUs (colony forming units) were determined by plating. Blood was also plated to determine the CFUs in the blood.

5. Pharmacokinetic Studies

The rate at which a compound of this invention is removed from the blood can be determined in either rats or mice. In rats, the test animals were cannulated in the jugular vein. The test compound was administered via tail vein injection, and at various time points (normally 5, 15, 30,60 minutes and 2,4,6 and 24 hours) blood was withdrawn from the cannula In mice, the test compound was also administered via tail vein injection, and at various time points. Blood was normally obtained by cardiac puncture. The concentration of the remaining test compound was determined by HPLC.

In general, the compounds of the invention were active in the above test in vivo and demonstrated a broad spectrum of activity.

Example 6

Determination of Tissue Accumulation

A. Tissue Distribution Using Radiolabeled Compound

This procedure is used to examine the tissue distribution, excretion and metabolism of a radiolabeled test compound in both male and female rats following intravenous infusion at 10 mg/kg. Male and female Sprague-Dawley rats (n =2 per sex per compound) are dosed with ^{3}H-labeled test compound at 10 (400 μCi/kg) and 12.5 mg/kg (100 μCi/kg), respectively, via intravenous infusion (~2 min). The test compound is formulated in 5% hydroxypropyl-β-cyclodextrin as 2.5 mg/ml solution. Urine and feces are cage collected over 24 hours period. At 24 hours after dosing, animals are sacrificed and tissues are removed. Serum, urine and tissues are analyzed for total radioactivity by oxidation followed by liquid scintillation counting. Urine and selected tissues samples are extracted and analyzed by reverse phase HPLC with radioactive flow detector for the presence of potential metabolites.

B. Tissue Accumulation Following Single Dose

This procedure is used to evaluate tissue distribution of a test compound in rats following single dose administration

by infusion. Male Sprague-Dawley rats (n =3 per dose groups) are dosed with 50 mg/kg of a test compound. Two formulations are used: 30% PEG 400 and 10% sulfobutylether-β-cyclodextrin. Urine samples are cage collected over 24 hours. Blood samples are collected for serum chemistry and concentration determination. Liver and kidneys are removed for histology evaluation. One kidney and part of the liver are homogenized for concentration analysis using reverse phase HPLC with UV detection. Drug concentrations in urine and serum samples are determined by LC-MS analysis.

C. Tissue Distribution Following Multiple Doses

This procedure is used to evaluate the potential tissue accumulation of a test compound in rats following multiple dose administration by intravenous infusion. Male and female Sprague-Dawley rats (n=4 per sex per dose group) are dosed with a test compound at 12.5, 25 and 50 mg/kg per day for seven days. Animals are sacrificed at day 1 (n=3 per sex per dose group) following the last dose administered. One animal per sex per dose group is retained as recovery animal and sacrificed at day 7 following the last dose administered. The test compound is formulated in 5% hydroxypropyl-β-cyclodextrin or 1% sucrose/4.5% dextrose. Urine samples are cage collected at days 1 and 7 post-dose. Blood samples are collected for serum chemistry and concentration determination. Liver and kidneys are removed for histology evaluation. One kidney and part of the liver are homogenized for concentration analysis using reverse phase HPLC with UV detection. Drug concentrations in urine and serum samples are determined by LC-MS analysis.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. Additionally, all publications, patents, and patent documents cited hereinabove are incorporated by reference herein in full, as though individually incorporated by reference.

What is claimed is:

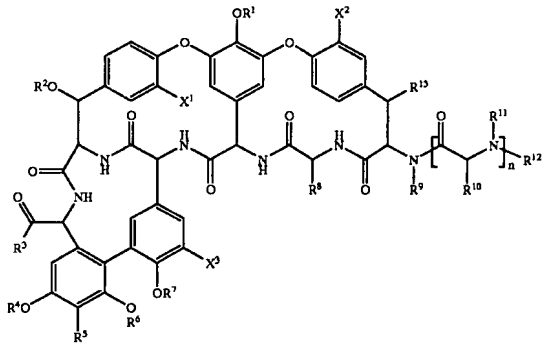
1. A glycopeptide substituted with one or more substituents each comprising one or more phosphono groups; or a pharmaceutically acceptable salt, or stereoisomer, or prodrug thereof.

2. A glycopeptide comprising a carboxy-terminus, wherein the glycopeptide is substituted at the carboxy-terminus with a substituent comprising one or two phosphono groups.

3. A glycopeptide comprising a 1,3-dihydroxyphenyl moiety, wherein the glycopeptide is substituted at the 2-position of the 1,3-dihydroxyphenyl moiety with a substituent comprising one or two phosphono groups.

4. The glycopeptide of claim 3, wherein the substituent is N-(phosphonomethyl)aminomethyl; N-(2-hydroxy(2-phosphonoethyl)aminomethyl; N-carboxymethyl-N-(phosphonomethyl)aminomethyl; N,N,-bis (phosphonomethyl)aminomethyl. or N-(3-phosphonopropyl)aminomethyl.

5. A glycopeptide of formula I:



wherein:

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $—R^a—Y—R^b—(Z)_x$; or R^1 is a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$;

R^2 is hydrogen or a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$;

R^3 is $—OR^c$, $—NR^cR^c$, $—O——R^a—Y—R^b—(Z)_x$, $—NR^c—R^a—Y—R^b—(Z)_x$, $—NR^cR^e$, or $—O—R^e$; or R^3 is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $—R^a—Y—R^b—(Z)_x$, $—C(O)R^d$ and a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, or $—C(O)—R^a—Y—R^b—(Z)_x$, or R^4 and R^5 can be joined, together with the atoms to which they are attached, to form a heterocyclic ring optionally substituted with $—NR^c—R^a—Y—R^b—(Z)_x$;

R^5 is selected from the group consisting of hydrogen, halo, $—CH(R^c)—NR^cR^c$, $—CH(R^c)—NR^cR^e$, $—CH(R^c)—NR^c—R^a—Y—R^b—(Z)_x$, $—CH(R^c)—R^x$, $—CH(R^c)—NR^c—R^a—C(=O)—R^x$, and a substituent that comprises one or more phosphono groups;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $—R^a—Y—R^b—(Z)_x$, $—C(O)R^d$ and a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$, or R^5 and R^6 can be joined, together with the atoms to which they are attached, to form a heterocyclic ring optionally substituted with $—NR^c—R^a—Y—R^b—(Z)_x$;

R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $—R^a—Y—R^b—(Z)_x$, and $—C(O)R^d$;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $—Ar^1—O—Ar^2—$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;

R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $—C(O)R^d$, $—C(NH)R^d$, $—C(O)NR^cR^c$, $—C(O)OR^d$, $—C(NH)NR^cR^c$, $—R^a—Y—R^b—(Z)_x$, and $—C(O)—R^a—Y—R^b—(Z)_x$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $—OR^{14}$;

R^{14} is selected from hydrogen, $—C(O)R^d$ and a saccharide group;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $—C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

each R^f is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, or heterocyclic;

R^x is an N-linked amino saccharide or an N-linked heterocycle;

X^1, X^2 and X^3 are independently selected from hydrogen or chloro; each Y is independently selected from the group consisting of oxygen, sulfur, —S—S—, $—NR^c—$, —S(O)—, $—SO_2$, $—NR^cC(O)—$, $—OSO_2—$, —OC(O)—, $—NR^cSO_2—$, $—C(O)NR^c—$, —C(O)O—, $—SO_2NR^c$, $—SO_2O—$, $—P(O)(OR^c)O—$, $—P(O)(OR^c)NR^c—$, $—OP(O)(OR^c)O—$, $—OP(O)(OR^c)NR^c—$, —OC(O)O—, $—NR^cC(O)O—$, $—NR^cC(O)NR^c—$, $—OC(O)NR^c$, —C(=O)—, and $—NR^cSO_2NR^c—$;

each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2; and

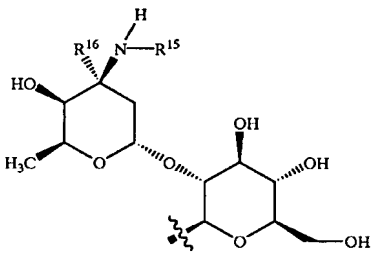
x is 1 or2;

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof;

provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.

6. The glycopeptide of claim **5** wherein R^1 is a saccharide group optionally substituted with $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)$.

7. The glycopeptide of claim **5** wherein R^1 is a saccharide group of the formula:



wherein R^{15} is $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$; and R^{16} is hydrogen or methyl.

8. The glycopeptide of claim **6** wherein R^2, R^4, R^6, and R^7 are each hydrogen.

9. The glycopeptide of claim **8** wherein R^3 is —OH.

10. The glycopeptide of claim **8** wherein R^3 is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups.

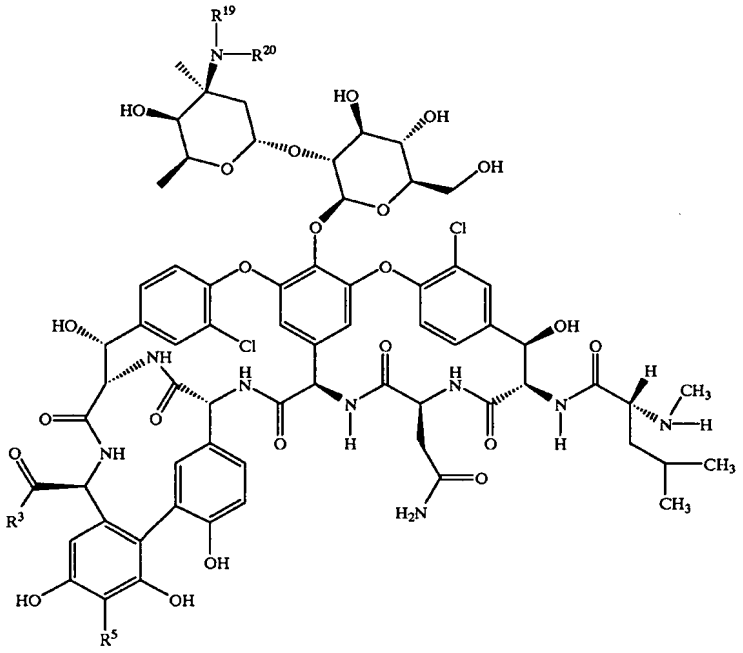
11. The glycopeptide of claim **10** wherein R^3 is a group of the formula $—O—R^a—P(O)(OH)_2$, $—S—R^a—P(O)(OH)_2$, or $—NR^c—R^a—P(O)(OH)_2$.

12. The glycopeptide of claim **8** wherein R^5 is a group of the formula $—CH(R^{21})—N(R^c)—R^a—P(O)(OH)_2$; wherein R^{21} is hydrogen or R^d.

13. The glycopeptide of claim **12** wherein R^5 is $—CH_2—NH—R^a—P(O)(OH)_2$.

14. The glycopeptide of claim **5** which is a compound of formula II:

(II)



wherein:

R^{19} is hydrogen;

R^{20} is $—R^a—Y—R^b—(Z)_x$, R^f, $—C(O)R^f$, or $—C(O)—R^a—Y—R^b—(Z)_x$; and

R^a, Y, R^b, Z, x, R^f, R^3, and R^5 have the values defined in claim **5**;

or a pharmaceutically acceptable salt, or stereoisomer, or prodrug thereof;

provided at least one of R^3 and R^5 is a substituent comprising one or more phosphono groups.

15. The glycopeptide of claim **14** wherein R^3 is —OH.

16. The glycopeptide of claim **14** wherein R^3 is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups.

17. The glycopeptide of claim **14** wherein R^3 is a group of the formula $—O—R^a—P(O)(OH)_2$, $—S—R^a—P(O)(OH)_2$, or $—NR^c—R^a—P(O)(OH)_2$.

18. The glycopeptide of claim **14** wherein R^5 is a group of the formula $—(CH(R^{21})—N(R^c)—R^a—P(O)(OH)_2$; wherein R^{21} is hydrogen or R^d.

19. The glycopeptide of claim **14** wherein R^{20} is $—CH_2CH_2—NH—(CH_2)_9CH_3$; $—CH_2CH_2CH_2—NH—(CH_2)_8CH_3$; $—CH_2CH_2CH_2CH_2—NH—(CH_2)_7CH_3$; $—CH_2CH_2—NHSO_2—(CH_2)_9CH_3$; $—CH_2CH_2—NHSO_2—(CH_2)_{11}CH_3$; $—CH_2CH_2—S—(CH_2)_8CH_3$; $—CH_2CH_2—S—(CH_2)_9CH_3$; $—CH_2CH_2—S—(CH_2)_{10}CH_3$; $—CH_2CH_2CH_2—S—(CH_2)_8CH_3$; $—CH_2CH_2CH_2—S—(CH_2)_9CH_3$; $—CH_2CH_2CH_2—S—(CH_2)_3—CH=CH—(CH_2)_4CH_3$ (trans); $—CH_2CH_2CH_2CH_2—S—(CH_2)_7CH_3$; $—CH_2CH_2—S(O)—(CH_2)_9CH_3$; $—CH_2CH_2—S—(CH_2)_6Ph$; $—CH_2CH_2—S—(CH_2)_8Ph$; $—CH_2CH_2CH_2—S—(CH_2)_8Ph$; $—CH_2CH_2—NH—CH_2$-4-(4-Cl—Ph)—Ph; $—CH_2CH_2—NH—CH_2$-4-[4-$(CH_3)_2CHCH_2$]—Ph; $—CH_2CH_2—NH—CH_2$-4-(4-CF_3—Ph)—Ph; $—CH_2CH_2—S—CH_2$-4-(4-Cl—Ph)—Ph; $—CH_2CH_2—S(O)—CH_2$-4-(4-Cl—Ph)—Ph; $—CH_2CH_2CH_2—S—CH_2$-4-(4-Cl—Ph)—Ph; $—CH_2CH_2CH_2—S(O)—CH_2$-4-(4-Cl—Ph)—Ph; $—CH_2CH_2CH_2—S—CH_2$-4-(3,4-di-Cl—PhCH_2O—)—Ph; $—CH_2CH_2—NHSO_2—CH_2$-4-[4-(4-Ph)—Ph]—Ph; $—CH_2CH_2CH_2—NHSO_2—CH_2$-4-(4-Cl—Ph)—Ph; $—CH_2CH_2CH_2—NHSO_2—CH_2$-4-(Ph—C≡C—)—Ph; $—CH_2CH_2CH_2—NHSO_2$-4-(4-Cl—Ph)—Ph; or $—CH_2CH_2CH_2—NHSO_2$-4-(naphth-2-yl)—Ph.

20. The glycopeptide of claim **14** wherein R^3 is —OH; R^5 is N-(phosphonomethyl)-aminomethyl; R^{19} is hydrogen, and R^{20} is $—CH_2CH_2—NH—(CH_2)_9CH_3$; or a pharmaceutically acceptable salt thereof.

21. The glycopeptide of claim **14** wherein R^3 is —OH; R^5 is N-(phosphonomethyl)-aminomethyl; R^{19} is hydrogen, and R^{20} is $—CH_2CH_2—NH—(CH_2)_9CH_3$.

22. The glycopeptide of claim **20** which is the hydrochloride salt.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a glycopeptide of any one of claims **1**, **5**, **14**, and **20**.

24. The pharmaceutical composition of claim **23**, which comprises a cyclodextrin.

25. The composition of claim **24** wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

26. The composition of claim **25** which comprises from about 250 mg to about 1000 mg of the glycopeptide and from about 250 mg to about 10 g hydroxypropyl-β-cyclodextrin.

27. The composition of claim **26** wherein the weight ratio of hydroxypropyl-β-cyclodextrin to the glycopeptide is from about 1:1 to about 10:1 inclusive.

28. A method for preparing a glycopeptide of claim **2**, comprising derivatizing a corresponding starting glycopeptide wherein the carboxy-terminus is a carboxy group.

29. A method for preparing a glycopeptide of claim **3**, comprising derivatizing a corresponding starting glycopep-

tide wherein the 2-position of the 1,3-dihydroxyphenyl moiety is unsubstituted.

30. A method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a therapeutically effective amount of a glycopeptide of any one of claims **1**, **5**, **14**, or **20**.

31. A method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition of claim **23**.

* * * * *

APPENDIX C

Copy of Related Documents

Patent Term Extension Application

for

U.S. Patent No. 6,635,618 B2

(Attorney Docket No. P-088-US1)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

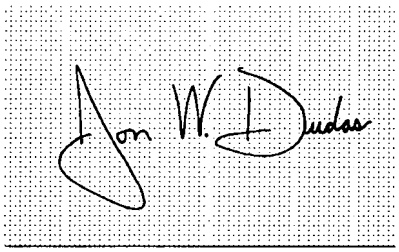
PATENT NO. : 6,635,618 B2
DATED : October 21, 2003
INVENTOR(S) : Leadbetter et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [*] Notice, change "88" days" to -- 144 days --.

Signed and Sealed this

Eighth Day of June, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,635,618 B2
DATED : October 21, 2003
INVENTOR(S) : Leadbetter et al.

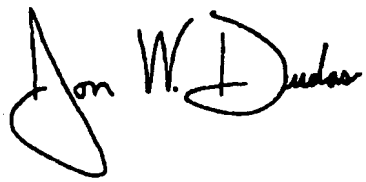
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 48,
Line 43, after "R^f,", please insert -- $-C(O)R^f$, --.

Column 50,
Line 9, please replace "$-SO_2$," with -- $-SO_2-$, --; and
Line 15, please replace "$-OC(O)NR^c$," with -- $-OC(O)NR^c-$, --.

Signed and Sealed this

First Day of November, 2005



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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,635,618	**$900.00**	**$0.00**	**04/23/07**	**09/847,042**	**10/21/03**	**05/01/01**	**04**	**NO**	**P-088-R**

APPENDIX D

Brief Description of Activities of Applicant During Regulatory Review Period

Patent Term Extension Application

for

U.S. Patent No. 6,635,618 B2

(Attorney Docket No. P-088-US1)

APPENDIX D

Brief Description of Activities of Applicant During Regulatory Review Period

Date	Brief Description of Activities
23 May 2002	Submitted IND Application No. 60,237
30 May 2002	Received FDA letter re: receipt of IND application
24 Jun 2002	Submitted change in regulatory contact information
25 Jun 2002	FDA Teleconference
26 Jun 2002	Submitted General Correspondence
28 Jun 2002	Submitted Pharmacology/Toxicology Amendment
03 Jul 2002	Submitted Information Amendment re: Clinical 201a CRF, DSMS Charter
15 Jul 2002	Received FDA facsimile re: comments on 28 Jun 2002 submission
24 Jul 2002	Received FDA memorandum re: 24 May 2002 teleconference
07 Aug 2002	Submitted Non-Clinical Safety Report re: Limb Malformations In Developmental Toxicity Studies
07 Aug 2002	Submitted Non-Clinical Safety Report re: Hep Tox in 3-Month Toxicity Studies
13 Aug 2002	Submitted Amendment re: Response to FDA 15 Jul 2002 Communication; GLP hERG; Draft CSR 102a; Draft CSR 102a Sub-Study; Safety and Pharmacokinetics of Intravenous TD-6424 in Healthy Subjects; Exploratory in Vitro Study on the Effects of AMI-6424 on Coagulation Assays; Exploratory Study of the Effect of TD-6424 on Platelet Aggregation in Vitro
27 Aug 2002	Received FDA facsimile re: 25 Jun 2002 teleconference minutes
12 Sep 2002	Received FDA telephone call re: initiation of Phase 1 Study on Safety and Pharmacokinetics of Intravenous TD-6424
14 Oct 2002	Submitted Clinical Amendment re: Safety And Pharmacokinetics of Intravenous TD-6424 In Healthy Subjects
15 Oct 2002	Received FDA facsimile re: comments on Phase 1 ECG protocol and microbiology
08 Nov 2002	Submitted response to 15 Oct 2002 FDA comments
21 Nov 2002	Submitted Protocol Amendment re: I6424-104a and 02-6424-BC-04
14 Jan 2003	Submitted Pharmacology Information Amendment re: Effects of AMI-6424 on hERG Tail Current Recorded from Stably Infected

Date	Brief Description of Activities
	HEK293 Cells; Effects of AMI-6424 on Action Potential Parameters in Dog Isolated Cardiac Purkinje Fibers; Effect of AMI-6424 on Action Potential Parameters in Sheep Isolated Cardiac Purkinje Fibers; A Cardiovascular Profile Study Following an Intravenous Infusion of AMI-6424 in the Conscious Unrestrained Beagle Dog; Tissue Distribution, Excretion and Metabolism Of ^{14}C-TD-6424 in Rats; Tissue Distribution, Excretion and Metabolism of ^{14}C-TD-6424 Following Intravenous Infusion to Dogs; Exploratory 7-Day Intravenous Toxicity Study with AMI-6424 in Male Rats; 4-Week Intravenous Infusion Toxicity Study with AMI-6424 in Rats with a 4-Week Recovery; 4-Week Intravenous Infusion Toxicity Study with AMI-6424 in Beagle Dogs with a 4-Week Recovery; *Salmonella-Escherichia Coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with AMI-6424; *Salmonella-Escherichia Coli*/Mammalian-Microsome Reverse Mutation Assay with AMI-6424 (Trifluoroacetic Acid Salt) Amended Final Report
15 Jan 2003	Submitted Clinical Amendment
19 Feb 2003	Received FDA facsimile re: Request For Additional Information
28 Feb 2003	Submitted response re: Request for Information and IND Protocol Amendment
08 Apr 2003	Submitted CMC Amendment
09 Apr 2003	Submitted Protocol Information Amendment re: Range-Finding Intravenous Injection Toxicity Study of AMI-6424 in Pregnant Female Rats; Range-Finding Intravenous Injection Toxicity Study of AMI-6424 in Non-Pregnant Female Rabbits; Range-Finding Intravenous Injection Toxicity Study of AMI-6424 in Pregnant Female Rabbits; Intravenous Injection Rat Developmental Toxicity Study with AMI-6424; and Intravenous Injection Rabbit Developmental Toxicity Study with AMI-6424
05 May 2003	Submitted Clinical Amendment
06 Jun 2003	Submitted Clinical Amendment
07 Jul 2003	Submitted Clinical Amendment
22 Jul 2003	Submitted IND Annual Report
05 Aug 2003	Submitted Clinical Amendment
03 Sep 2003	Submitted Clinical Amendment
15 Sep 2003	Submitted Safety Report

Date	Brief Description of Activities
23 Oct 2003	Submitted Clinical Amendment
07 Nov 2003	Submitted Request for Pre-Phase 3 Meeting
13 Nov 2003	Submitted Clinical Amendment
19 Nov 2003	Submitted Protocol Information Amendment re: 13-Week Intravenous Infusion Toxicity Study with AMI-6424 in Rats with a 4-Week Recovery; Intravenous Injection Study of Fertility and Early Embryonic Development to Implantation with AMI-6424 in Rats; Intravenous Injection Rabbit Developmental Toxicity Study with AMI-6424; Intravenous Injection Study for Effects on Pre- and Postnatal Development, Including Maternal Function, with AMI-6424 in the Rat; 2-Week Intravenous Infusion Toxicity Study with AMI-6424 in Beagle Dogs with a 2-Week Recovery
21 Nov 2003	Submitted Clinical Safety Report
04 Dec 2003	Submitted letter suspending enrollment in Study 203a, Amendment 2
08 Dec 2003	Submitted Clinical Amendment
09 Dec 2003	Submitted Information Amendment re: microbiology protocol for Rabbit Endocarditis Study Report
11 Dec 2003	FDA Teleconference
11 Dec 2003	Submitted Clinical Information Amendment re: summary of Clinical PK
11 Dec 2003	Submitted pharmacology Information Amendment re: draft A 13-week Intravenous Infusion Toxicity Study (with a 28-Day Recovery Period) of AMI-6424 in the Beagle Dog
17 Dec 2003	Submitted Clinical Information Amendment re: blinded patient data from FAST study
12 Jan 2004	Submitted Clinical Amendment
27 Jan 2004	Received FDA minutes for 11 Dec 2003 teleconference
29 Jan 2004	Submitted Pharmacology Information Amendment re: final A 13-week Intravenous Infusion Toxicity Study (with a 28-Day Recovery Period) of AMI-6424 in the Beagle Dog
05 Feb 2004	Submitted draft Clinical Protocol (0015)
10 Feb 2004	Submitted Clinical Amendment
01 Mar 2004	Submitted Clinical Safety Report

Date	Brief Description of Activities
02 Mar 2004	Submitted Clinical Amendment
29 Mar 2004	Submitted Clinical Safety Report
29 Mar 2004	Submitted Clinical Amendment
30 April 2004	Submitted Request for End-of-Phase 2 Meeting
14 May 2004	Received FDA letter requesting meeting re: Phase 3 development plan for telavancin
21 May 2004	Submitted Clinical Amendment
21 May 2004	Submitted Request for Review of Proprietary Names
26 May 2004	Submitted Pharmacology Information Amendment re: 6 Week Intravenous Injection Study of Potential Gonadal Effects and Reversibility with AMI-6424 in Male Rats with an 8 Week Recovery Period
26 May 2004	Received FDA letter re: End-of-Phase 2 Meeting
04 Jun 2004	Submitted General Correspondence re: use of Lot No. AME009
04 Jun 2004	Submitted General Correspondence re: End-of-Phase 2 Meeting Notification
04 Jun 2004	Submitted Clinical Information
10 Jun 2004	Submitted End-of-Phase 2 Meeting Information Package
17 Jun 2004	Submitted Clinical Safety Report
18 Jun 2004	Received FDA facsimile re: request for information regarding renal dosing nomogram
18 Jun 2004	Received FDA facsimile re: reviewer's comments on clinical pharmacology
23 Jun 2004	Submitted response to FDA 18 Jun 2004 Request for Information
23 Jun 2004	Submitted New Protocols (0018 and 0017) and Protocol Amendment
25 Jun 2004	Submitted General Correspondence re: pig teratology study
28 Jun 2004	Submitted Clinical Safety Report
02 Jul 2004	Submitted Clinical Safety Report
06 Jul 2004	Submitted Investigator Updates
12 Jul 2004	End-of-Phase 2 Meeting
16 Jul 2004	Submitted End-of-Phase 2 Meeting Information Package re: CMC

Date	Brief Description of Activities
19 Jul 2004	Submitted Clinical Safety Report
19 Jul 2004	Received FDA memorandum re: comments on Clinical End-of-Phase 2 Briefing Package
21 Jul 2004	Submitted New Protocol re: Hepatic Impairment (0016) and Investigator Updates
23 Jul 2004	Submitted response to FDA reviewers' comments and Revised Protocols (0017, 0018)
23 Jul 2004	Submitted Annual Report
05 Aug 2004	Submitted Clinical Safety Report
13 Aug 2004	Submitted response to FDA reviewers' comments and Revised Protocols (0015, 0019)
13 Aug 2004	Received FDA memorandum re: comments on CMC End-of-Phase 2 Briefing Package
13 Aug 2004	Received FDA facsimile re: comments on sponsor's questions (Section 8.1 and 8.2)
25 Aug 2004	Submitted Pharmacology Amendment re: draft 26-Week Intravenous Infusion Toxicity and Toxicokinetic Study with AMI-6424 in Rats with a 4-Week Recovery Period
14 Sep 2004	Submitted Investigator Information for 0017
20 Sep 2004	Received FDA letter re: minutes for CMC End-of-Phase 2 Meeting
23 Sep 2004	Submitted Investigator Update
04 Nov 2004	Submitted IND Safety Report
15 Nov 2004	Submitted Investigator Update
14 Dec 2004	Submitted Investigator Update
15 Dec 2004	Received FDA facsimile re: questions on 0015 and 0019
16 Dec 2004	Received FDA letter re: End-of-Phase 2 Meeting
17 Dec 2004	Submitted IND Safety Report
20 Dec 2004	Submitted IND Safety Report
22 Dec 2004	Submitted Protocol Amendments for 0017 and 0018
05 Jan 2005	Submitted Information Amendment re: microbiology
14 Jan 2005	Received FDA End-of-Phase 2 Meeting Minutes

Date	Brief Description of Activities
19 Jan 2005	Submitted IND Safety Report
02 Feb 2005	Submitted Request for Fast Track Designation
10 Feb 2005	Received FDA Notice of Receipt of Request for Fast Track Designation
16 Feb 2005	Submitted Investigator Update
17 Feb 2005	Submitted Response to FDA Request for Information
17 Feb 2005	Submitted IND Safety Report
22 Feb 2005	Submitted IND Safety Report
23 Feb 2005	Submitted Request for Review of Proprietary Names (Resubmission)
28 Feb 2005	Submitted IND Safety Report
28 Feb 2005	Submitted IND Safety Report
18 Mar 2005	Submitted Investigator Update
14 Mar 2005	Submitted IND Safety Report
24 Mar 2005	Received FDA letter granting Fast Track Designation
14 Apr 2005	Submitted IND Safety Report
19 Apr 2005	Submitted Investigator Update
22 Apr 2005	Received FDA comments re: 0015 and 0019 protocols
02 May 2005	Submitted IND Safety Report
09 May 2005	FDA Teleconference
20 May 2005	Submitted IND Safety Report
27 May 2005	Submitted IND Safety Report
03 Jun 2005	Submitted IND Safety Report
06 Jun 2005	Submitted Investigator Update
21 Jun 2005	Received FDA letter re: Minutes for 09 May 2005 Teleconference
24 Jun 2005	Submitted IND Safety Report
15 Jul 2005	Submitted IND Safety Report
25 Jul 2005	Submitted IND Safety Report
01 Aug 2005	Submitted IND Safety Report
01 Aug 2005	Submitted IND Safety Report

Date	Brief Description of Activities
02 Aug 2005	Submitted IND Safety Report
05 Aug 2005	Submitted IND Safety Report
05 Aug 2005	Submitted Investigator Update
05 Aug 2005	Submitted IND Safety Report
16 Aug 2005	Submitted IND Safety Report
23 Aug 2005	Submitted IND Safety Report
29 Aug 2005	Submitted IND Safety Report
30 Aug 2005	Submitted IND Safety Report
01 Sep 2005	Submitted IND Safety Report
06 Sep 2005	Submitted IND Safety Report
06 Sep 2005	Submitted IND Annual Report
13 Sep 2005	Submitted IND Safety Report
20 Sep 2005	Submitted Investigator Update and New Protocol
20 Sep 2005	Submitted IND Protocol Amendment
21 Sep 2005	Submitted Pharmacology/Toxicology Information Amendment
27 Sep 2005	Submitted IND Safety Report
05 Oct 2005	Submitted IND Safety Report
06 Oct 2005	Submitted IND Safety Report
10 Oct 2005	Submitted IND Safety Report
14 Oct 2005	Submitted IND Safety Report
17 Oct 2005	Submitted Request for Meeting
20 Oct 2005	Submitted IND Safety Report
21 Oct 2005	Submitted IND Safety Report
28 Oct 2005	Submitted IND Safety Report
31 Oct 2005	Submitted IND Safety Report
01 Nov 2005	Received FDA letter re: Request for Pre-NDA Meeting
04 Nov 2005	Submitted Protocol Amendments and Information Amendment
04 Nov 2005	Received FDA facsimile re: request for reproductive teratology study and information

Date	Brief Description of Activities
04 Nov 2005	Submitted IND Safety Report
08 Nov 2005	Submitted Response to Request for Information
15 Nov 2005	Submitted IND Safety Report
16 Nov 2005	Submitted Request for CMC Pre-NDA Meeting
16 Nov 2005	Submitted General Correspondence re: Withdrawal of Proposed Tradenames
16 Nov 2005	Submitted Clinical/Safety/Microbiology Pre-NDA Meeting Information Package
16 Nov 2005	Submitted IND Safety Report
17 Nov 2005	Submitted IND Safety Report
21 Nov 2005	Submitted Response to Request for Information re: SAE Queries
22 Nov 2005	Submitted IND Safety Report
23 Nov 2005	Submitted IND Safety Report
28 Nov 2005	Submitted IND Safety Report
28 Nov 2005	Submitted IND Safety Report
29 Nov 2005	Submitted IND Safety Report
30 Nov 2005	Submitted IND Safety Report
01 Dec 2005	Submitted IND Safety Report
02 Dec 2005	Submitted IND Safety Report
05 Dec 2005	Received FDA facsimile re: comments on Clinical Microbiology
06 Dec 2005	Submitted IND Safety Report
09 Dec 2005	Submitted IND Safety Report
13 Dec 2005	Received FDA facsimile re: pre-meeting comments
14 Dec 2005	Submitted CMC Pre-NDA Meeting Information Package
19 Dec 2005	Submitted IND Safety Report
20 Dec 2005	Received FDA letter re: request for meeting on CMC topics
21 Dec 2005	Submitted Information Amendment
23 Dec 2005	Submitted IND Safety Report
03 Jan 2006	Submitted IND Safety Report

Date	Brief Description of Activities
04 Jan 2006	Submitted IND Safety Report
05 Jan 2006	Submitted IND Safety Report
06 Jan 2006	Submitted Information Amendment re: Microbiology
06 Jan 2006	Submitted IND Safety Report
12 Jan 2006	Submitted IND Safety Report
13 Jan 2006	Received FDA letter re: Pre-NDA Meeting
17 Jan 2006	Submitted Information Amendment re: Microbiology
17 Jan 2006	Received FDA letter re: Pre-NDA Meeting and comments relating to microbiology
18 Jan 2006	Submitted IND Safety Report
19 Jan 2006	Submitted IND Safety Report
23 Jan 2006	Submitted IND Safety Report
25 Jan 2006	Submitted IND Safety Report
26 Jan 2006	Submitted IND Safety Report
27 Jan 2006	Submitted IND Safety Report
30 Jan 2006	Submitted IND Safety Report
02 Feb 2006	Submitted IND Safety Report
02 Feb 2006	Submitted Pre-NDA Meeting Slides
03 Feb 2006	Submitted IND Safety Report
06 Feb 2006	Submitted IND Safety Report
09 Feb 2006	Submitted IND Safety Report
10 Feb 2006	Submitted IND Safety Report
14 Feb 2006	Submitted IND Safety Report
15 Feb 2006	Submitted Response re: Clinical Pre-NDA Meeting Questions
15 Feb 2006	Submitted IND Safety Report
13 Jan 2006	Received FDA letter re: Pre-NDA Meeting
17 Feb 2006	Submitted Protocol Amendment
17 Feb 2006	Submitted IND Safety Report
24 Feb 2006	Submitted IND Safety Report

Date	Brief Description of Activities
03 Mar 2006	Submitted Information Amendment re: Pharmacology/Toxicology
03 Mar 2006	Submitted IND Safety Report
03 Mar 2006	Submitted General Correspondence
03 Mar 2006	Submitted General Correspondence
03 Mar 2006	Received FDA letter re: Minutes of 01 Feb 2006 CMC Meeting
07 Mar 2006	Submitted IND Safety Report
09 Mar 2006	Submitted IND Safety Report
13 Mar 2006	Submitted IND Safety Report
24 Mar 2006	Submitted Protocol Amendment
24 Mar 2006	Submitted IND Safety Report
05 Apr 2006	Submitted IND Safety Report
06 Feb 2006	Received FDA facsimile re: comments from Clinical Microbiology Review Team
07 Apr 2006	Submitted Request for a Type B Meeting
14 Apr 2006	Submitted IND Safety Report
17 Apr 2006	Received FDA letter re: Request for Type B Meeting
21 Apr 2006	Submitted IND Safety Report
28 Apr 2006	Submitted Type B Meeting Package
28 Apr 2006	Submitted Response to Request for Information re: Microbiology
02 May 2006	Received FDA facsimile re: Biopharmaceutics Reviewer Comments
05 May 2006	Submitted IND Safety Report
31 May 2006	Received FDA facsimile re: Pre-Meeting Comments
10 May 2006	Submitted General Correspondence re: Planned NDA Data Submission
19 May 2006	Submitted IND Safety Report
23 May 2006	Submitted IND Safety Report
31 May 2006	Received FDA facsimile re: Pre-Meeting Comments
07 Jun 2006	Received FDA facsimile re: Clinical Microbiology Reviewer Comment
09 Jun 2006	Submitted IND Safety Report

Date	Brief Description of Activities
15 Jun 2006	Submitted IND Safety Report
23 Jun 2006	Submitted General Correspondence re: Oxacillin Comparator
23 Jun 2006	Submitted IND Safety Report
23 Jun 2006	Received FDA facsimile re: Comments on 01 Jun 2006 Meeting
28 Jun 2009	Received FDA letter re: 01 Jun 2006 Meeting Minutes
30 Jun 2006	Submitted IND Safety Report
30 Jun 2006	Submitted Protocol Amendment
12 Jul 2006	Submitted IND Safety Report
13 Jul 2006	Submitted IND Safety Report
21 Jul 2006	Submitted IND Safety Report
28 Jul 2006	Submitted General Correspondence
01 Aug 2006	Submitted IND Safety Report
08 Aug 2006	Submitted Information Amendment re: Clinical
18 Aug 2006	Submitted IND Safety Report
22 Aug 2006	Submitted General Correspondence re: Phase 3 Press Release
31 Aug 2006	Submitted IND Safety Report
01 Sep 2006	Received FDA facsimile re: Medical Officer's Comments
05 Sep 2006	Received FDA facsimile re: response from DAIOP
06 Sep 2006	Telephone request for NDA number (No. 22-110 assigned)
07 Sep 2006	Submitted Request for User Fee Waiver
08 Sep 2006	Submitted IND Safety Report
14 Sep 2006	Received copy of FDA request to SBA re: determination of Theravance size
15 Sep 2006	Received SBA letter re: request for THRX size information
19 Sep 2006	Received FDA facsimile re: comments and information requests from DAIOP
29 Sep 2006	Submitted General Correspondence re: Filing Format
29 Sep 2006	Submitted IND Safety Report
18 Oct 2006	Submitted Request for Waiver

Date	Brief Description of Activities
19 Oct 2006	Submitted Request for Meeting
25 Oct 2006	Submitted Annual Report and Investigator's Brochure
03 Nov 2006	Submitted IND Safety Report
03 Nov 2006	Submitted sample dataset for review
10 Nov 2006	Submitted New Protocol, New Investigator, and Transfer of Obligations
10 Nov 2006	Submitted IND Safety Report
15 Nov 2006	Submitted second sample dataset for review
21 Nov 2006	Submitted Module 3 and corresponding M1 & M2 documents (Presubmission)
21 Nov 2006	Submitted CMC documents (Presubmission)
22 Nov 2006	Received FDA facsimile re: Notice of SBA Determination of Theravance Size
22 Nov 2006	Submitted Notice of SBA Determination of Theravance Size
22 Nov 2006	Submitted Small Business Determination for User Fee Waiver
27 Nov 2006	Submitted Field Copy (Module 3) to SF District Office
04 Dec 2006	Submitted General Correspondence re: Brand Name Submission
07 Dec 2006	Submitted NDA Application No. 22-110
12 Dec 2006	Received FDA telephone request re: blinded CRFs
13 Dec 2006	Received FDA email request re: random samples for blinded CRFs
15 Dec 2006	Submitted Reviewer's Guide to Data for NDA 22-110
15 Dec 2006	Submitted request to withdraw presubmission
19 Dec 2006	Submitted blinded CRFs
19 Dec 2006	Received FDA letter re: NDA 22-110
20 Dec 2006	Received FDA letter re: request for Establishment Information
21 Dec 2006	Submitted Establishment Information
04 Jan 2007	Submitted Protocol Amendment re: New Investigator
04 Jan 2007	Submitted IND Safety Report
10 Jan 2007	Received FDA facsimile re: Small Business Waiver Request
11 Jan 2007	Received FDA email re: CRF questions and meeting request

Date	Brief Description of Activities
11 Jan 2007	Submitted response to request for meeting
11 Jan 2007	Received FDA email re: request for Non-Inferiority Margin Justification
16 Jan 2007	Submitted response re: CRFs
16 Jan 2007	Received FDA email re: CRFs for Site 38101
17 Jan 2007	Received notice of waiver for NDA 22-110 application fee
18 Jan 2007	Received FDA facsimile re: changes to Investigator's Brochure, Edition 7
22 Jan 2007	Submitted response re: CRFs for Site 38101
22 Jan 2007	Submitted request for information re: ECG data
22 Jan 2007	Received FDA email re: meeting to discuss QT consultant review aids
22 Jan 2007	Submitted response re: meeting to discuss QT consultant review aids
23 Jan 2007	Submitted IND Safety Report
23 Jan 2007	Submitted response re: CRFs
24 Jan 2007	Received FDA telephone call re: site information for GCP audits
26 Jan 2007	Submitted IND Safety Report
30 Jan 2007	Submitted response re: timeline for response
30 Jan 2007	Received FDA email re: notification study ID 0017 is ready for review
30 Jan 2007	Received FDA email re: notification study ID 0018 is ready for review
31 Jan 2007	Submitted General Correspondence
31 Jan 2007	Submitted response re: ECGs
31 Jan 2007	Received FDA email re: SPL submission
31 Jan 2007	Submitted response re: SPL submission
02 Feb 2007	Received FDA email re: confirmation of two Phase 3 studies (0017 and 0018) and two Phase 2 studies (202a and 202b)
06 Feb 2007	Submitted request for information re: CMC
07 Feb 2007	Submitted response re: Non-Inferiority Margin
12 Feb 2007	Submitted request for information re: BVL DMF 2315

Date	Brief Description of Activities
13 Feb 2007	Submitted General Correspondence re: IB/ICF Changes
16 Feb 2007	Submitted General Correspondence
16 Feb 2007	Received FDA email re: Status of Filing Communication for NDA 22-110
16 Feb 2007	Received FDA email re: IRT/QT Consultant Request for Information
20 Feb 2007	Received FDA email re: Filing Communication for NDA 22-110
22 Feb 2007	Submitted IND Safety Report
22 Feb 2007	Received FDA letter re: Acceptance of Telavancin NDA submission
23 Feb 2007	Submitted Stability Update Reports
26 Feb 2007	Received FDA facsimile re: Filing Communication completed for telavancin
27 Feb 2007	Submitted response re: Stability Data for Drug Substance
27 Feb 2007	Submitted response re: BVL DMF 2315
01 Mar 2007	Received FDA facsimile re: SPL/PLR Review
01 Mar 2007	Submitted Filter Validation Report and protocol for next NDA update
07 Mar 2007	Submitted Clinical Microbiology Amendment
09 Mar 2007	Submitted Quality Amendment re: BVL DMF 2315
09 Mar 2007	Submitted Clinical Microbiology Amendment
10 Mar 2007	Submitted information re: Phase 2 isolates and CMC
12 Mar 2007	Received FDA email re: NDA 22-110 submissions
16 Mar 2007	Submitted 104a data and documentation (CD ROM)
19 Mar 2007	FDA Teleconference
19 Mar 2007	Submitted NDA under Section 505(b)
23 Mar 2007	Received FDA letter re: memorandum of teleconference
30 Mar 2007	Submitted IND Safety Report
02 Apr 2007	Received FDA facsimile re: request for information from the clinical microbiology review team
06 Apr 2007	Received FDA facsimile re: request for information from the PK group
10 Apr 2007	Received FDA email re: request for additional PK dataset

Date	Brief Description of Activities
17 Apr 2007	Submitted General Correspondence
17 Apr 2007	Submitted tradename information and safety update
20 Apr 2007	Received FDA facsimile re: request for information on CMC
25 Apr 2007	Received FDA facsimile re: request for information from product quality microbiologist
26 Apr 2007	Submitted response to request for PK information
01 May 2007	Received FDA facsimile re: request for information from Maternal Health Team
01 May 2007	Received FDA facsimile re: request for information from CMC reviewer
02 May 2007	Received FDA email re: request for clarification
03 May 2007	Submitted response re: Non-Inferiority Margin Justification
04 May 2007	Submitted response re: request for information from Maternal Health Team
04 May 2007	Submitted response re: Non-Inferiority Margin Justification
08 May 2007	Submitted response re: Stability Data for Drug Substance
11 May 2007	Received FDA facsimile re: request for information from Maternal Health Team
21 May 2007	Submitted Patent Information
22 May 2007	Submitted response re: PK and Pharmacometrics
22 May 2007	Submitted response re: CMC
24 May 2007	Submitted response re: Clinical Microbiology
29 May 2007	Received FDA email re: request for information on Non-Inferiority Margin references
29 May 2007	Received FDA email re: request for information on IB for cardio consult
29 May 2007	Submitted response re: IB for cardio
30 May 2007	Submitted response re: Correction to references in Non-Inferiority Margin
05 Jun 2007	Submitted Protocol Amendment re: Transfer of Obligations
05 Jun 2007	Received FDA email re: status of Microsterility Studies

Date	Brief Description of Activities
06 Jun 2007	Submitted response re: Clinical Microbiology
07 Jun 2007	Submitted response re: CMC
11 Jun 2007	Submitted response re: CMC
19 Jun 2007	Submitted Proposed Pediatric Study Request
19 Jun 2007	Submitted request for meeting re: Pregnancy Category
21 Jun 2007	Submitted response re: Product Labeling
25 Jun 2007	Received FDA email re: request for information on Bioanalytical Report
27 Jun 2007	Received FDA email re: Pregnancy Category Meeting
28 Jun 2007	Submitted Pregnancy Category Meeting Briefing Document
03 Jul 2007	Submitted IND Safety Report
07 Jul 2007	Received FDA email re: request for information on CMC
13 Jul 2007	Received FDA email re: request for information on CMC
16 Jul 2007	Received FDA email re: request for information from PK reviewers
18 Jul 2007	Submitted Request for End-of-Phase 2 Meeting
20 Jul 2007	Submitted Response to request from Maternal Health Team
23 Jul 2007	Received FDA email re: request for information on CMC Non-Conformance Report NC06-002
25 Jul 2007	Submitted response re: CMC Non-Conformance Report NC06-002
30 Jul 2007	Received FDA email re: request for information on Alternate Analyses Variables
31 Jul 2007	Submitted response re: request for information on Alternate Analyses Variables
02 Aug 2007	Submitted Revised ISS Table 7-6
07 Aug 2007	Submitted response re: CMC
07 Aug 2007	Received FDA email re: Request for Clinical Pharmacology data relating to dose for Monte Carlo Simulation
07 Aug 2007	Received FDA email re: Tradename
08 Aug 2007	Received FDA email re: Request for clinical endpoint data clarification
10 Aug 2007	Received FDA email re: BVL status

Date	Brief Description of Activities
10 Aug 2007	Submitted response re: clinical data request
10 Aug 2007	Submitted response re: Vancomycin PK Safety
16 Aug 2007	Submitted response re: Clinical Pharmacology
21 Aug 2007	FDA Meeting
21 Aug 2007	Submitted response re: request for definition of clinical/pregnancy population
24 Aug 2007	Received FDA email re: request for slides from 21 Aug 2007 meeting
24 Aug 2007	Submitted response re: request for slides
27 Aug 2007	Submitted response re: Clinical Pharmacology request
29 Aug 2007	Submitted Annual Report and updated Investigator's Brochure
29 Aug 2007	Received FDA email re: Section 6.1 of the Proposed Label
30 Aug 2007	Submitted request re: PI Safety Table Revision
30 Aug 2007	Received FDA email re: Request for ECG data clarification
30 Aug 2007	Submitted request re: BVL status
31 Aug 2007	Submitted response re: Tradename
31 Aug 2007	Received FDA email re: BVL status
31 Aug 2007	Received FDA email re: Tradename
01 Sep 2007	Received FDA email re: BVL status
05 Sep 2007	Received FDA email re: request for dose change information
07 Sep 2007	Submitted response re: ECG request
13 Sep 2007	Submitted response re: PI Safety Table revision request
13 Sep 2007	Submitted response re: Clinical
14 Sep 2007	Submitted response re: Tradename
21 Sep 2007	Received FDA email re: Request for Microbiology Labeling Review
24 Sep 2007	Received FDA email re: Request for Safety Table footnote clarification
26 Sep 2007	Submitted response re: Safety Table footnote clarification
26 Sep 2007	BVL compliance note
27 Sep 2007	Submitted response re: dose change request

Date	Brief Description of Activities
28 Sep 2007	Submitted response re: Microbiology Label Review
01 Oct 2007	Submitted response re: Microbiology Label Review (corrected copy)
04 Oct 2007	Received FDA email re: Tradename
07 Oct 2007	Submitted response re: Proposed Label
09 Oct 2007	Received FDA email re: Request for updated financial disclosure data
10 Oct 2007	Submitted response re: request for updated financial disclosure data
11 Oct 2007	Submitted request re: confirmation of approved specification and expiration dating
15 Oct 2007	Submitted request re: teleconference on status of NDA review
16 Oct 2007	Received FDA email re: request for teleconference
17 Oct 2007	Submitted information re: Benefit/Risk Assessment
17 Oct 2007	Received FDA email re: Compliance Issue
18 Oct 2007	Submitted NDA attachments
19 Oct 2007	Received FDA email re: Action Letter for NDA
23 Oct 2007	Received Letter from Department of Health and Human Services re: EIR GMP Inspection
24 Oct 2007	Submitted Intent to Amend and Request for End of Review Conference (Type A Meeting)
26 Oct 2007	Received FDA email re: Post-Action Teleconference
29 Oct 2007	Received FDA email re: Teleconference
05 Nov 2007	Submitted End of Review Conference Briefing Package
20 Nov 2007	Received FDA email re: BVL Warning Letter
27 Nov 2007	Received FDA letter re: memorandum of meeting minutes
27 Nov 2007	Received FDA email re: Advisory Committee Meeting for Telavancin
27 Nov 2007	Received FDA letter re: Official Meeting Minutes
28 Nov 2007	Received FDA email re: Advisory Committee Meeting Briefing Documents
17 Dec 2007 to 14 Jan 2008	Received FDA emails re: FDA Advisory Committee Planning
16 Jan 2008	Received FDA email re: Request for teleconference to discuss

Date	Brief Description of Activities
	Advisory Committee issues
16 Jan 2008	FDA Teleconference
21 Jan 2008	Submitted amendment to Complete Response to Action Letter
22 Jan 2008	Submitted Waiver Request for Electronic Submissions
23 Jan 2008	Submitted email re: Clarification of Re-Analysis
24 Jan 2008	Received FDA email re: Clarification of Re-Analysis
25 Jan 2008	Received FDA email re: Waiver Request for Electronic Submissions
28 Jan 2008	Submitted Advisory Committee Briefing Document
28 Jan 2008	Received FDA email re: Re-Analysis
28 Jan 2008	Submitted response re: Re-Analysis
30 Jan 2008	Received FDA email re: Advisory Committee Briefing Document
30 Jan 2008	Submitted response re: Advisory Committee Briefing Document
31 Jan 2008	Submitted response re: Advisory Committee Briefing Document
01 Feb 2008	Received FDA email re: Advisory Committee Briefing Document
03 Feb 2008	Submitted Revised Advisory Committee Briefing Document
04 Feb 2008	Received FDA email re: Revised Advisory Committee Briefing Document
05 Feb 2008	Received FDA letter re: FDA Briefing Document
07 Feb 2008	Received FDA email re: FDA Populations Outcomes
08 Feb 2008	FDA Teleconference
09 Feb 2008	Submitted request re: FDA Briefing Document Availability Consultants
11 Feb 2008	Received FDA email re: FDA Briefing Document Availability Consultants
12 Feb 2008	Submitted Amendment to Quality Information
12 Feb 2008	Received FDA email re: FDA Briefing Document Availability Consultants
15 Feb 2008	Received FDA email re: Meeting Agenda/Presenters
19 Feb 2008	Submitted response re: Meeting Agenda/Presenters
22 Feb 2008	Submitted Study Site(s) Inquiry

Date	Brief Description of Activities
22 Feb 2008	Received FDA email re: Study Site(s) Inquiry
23 Feb 2008	Submitted request re: Teleconference
23 Feb 2008	FDA Teleconference
23 Feb 2008	Submitted Briefing Document Posting
23 Feb 2008	Received FDA email re: Briefing Document Posting
24 Feb 2008	Received FDA email re: Press Release on Cancellation of Advisory Committee Meeting
24 Feb 2008	Submitted response re: Press Release
25 Feb 2008	FDA Teleconference
25 Feb 2008	Received FDA email re: Information Request
25 Feb 2008	FDA Teleconference
25 Feb 2008	Submitted response re: Information Request
27 Feb 2008	Meeting with FDA
28 Feb 2008	Submitted response re: formatting issue for Approvable Letter
29 Feb 2008	Received FDA email re: Pediatric Drug Development Plan
29 Feb 2008	Submitted response re: Pediatric Drug Development Plan
04 Mar 2008	Received FDA acknowledgement letter re: Class 2 Resubmission
05 Mar 2008	Received FDA email re: Microsterility
17 Mar 2008	Received FDA email re: request for information on clinical site
17 Mar 2008	Submitted response re: request for information on clinical site
18 Mar 2008	Received FDA email re: request for information US clinical sites
18 Mar 2008	Submitted response re: request for information US clinical sites
20 Mar 2008	Received FDA email re: request for information on clinical site
21 Mar 2008	Submitted response re: request for information on clinical site
24 Mar 2008	FDA Teleconference
25 Mar 2008	Received FDA email re: Meeting
25 Mar 2008	Submitted response re: Meeting
26 Mar 2008	Submitted response re: Clinical Data Monitoring Questions
02 Apr 2008	Submitted response re: DSI-Request-DAIOP-Copy

Date	Brief Description of Activities
04 Apr 2008	Received FDA email re: Meeting Agenda
04 Apr 2008	Submitted response re: Meeting Agenda
14 Apr 2008	Submitted Patent Information
16 Apr 2008	Meeting with FDA
09 May 2008	Received FDA email re: request for information from Division of Scientific Investigations (DSI).
06 Aug 2008	Received FDA email re: Status Update
06 Aug 2008	Submitted response re: Status Update
06 Aug 2008	Submitted response re: Telavancin Studies 0017 and 0018
12 Aug 2008	Received FDA letter re: Telavancin PLR Label
12 Aug 2008	Submitted response re: Telavancin PLR Label
21 Aug 2008	Received FDA email re: Investigator List for Advisory Committee Meeting
22 Aug 2008	Submitted supplemental response re:Telavancin Studies 0017 and 0018
03 Sep 2008	Submitted Request for Meeting
04 Sep 2008	Received FDA email re: Request for meeting
04 Sep 2008	Received FDA email re: Pediatric Plan
08 Sep 2008	Submitted response re: Pediatric Plan
17 Sep 2008	Received FDA email re: Teleconference
17 Sep 2008	Submitted response re: Teleconference
18 Sep 2008	Received FDA email re: Information Request
22 Sep 2008	Submitted response re: Request for Pediatric Plan
22 Sep 2008	FDA Teleconference
23 Sep 2008	Submitted Pediatric Program
23 Sep 2008	Received FDA email re: Telavancin Carton and Container Label
24 Sep 2008	Submitted response re: Request for Information
24 Sep 2008	Received FDA email re: Pediatric Program
25 Sep 2008	Received FDA email re: Advisory Committee Meeting
25 Sep 2008	Submitted response re: Pediatric Plan

Date	Brief Description of Activities
29 Sep 2008	Received FDA email re: Pediatric Plan
29 Sep 2008	Received FDA email re: Microbial Challenge Study
29 Sep 2008	Submitted response re: Microbial Challenge Study
29 Sep 2008	Received FDA email re: Advisory Committee Meeting
30 Sep 2008	Submitted response re: Selected Re-Analyses of Studies 0017 and 0018
30 Sep 2008	Received FDA email re: Re-Analysis
01 Oct 2008	Received FDA email re: CMC Labeling Comments
10 Oct 2008	Submitted Annual Report
10 Oct 2008	Submitted response re: Request for Information
14 Oct 2008	Received FDA email re: Advisory Committee Meeting
15 Oct 2008	Submitted Advisory Committee Briefing Document
27 Oct 2008	Received FDA email re: Carton and Container Label
28 Oct 2008	Submitted response re: Carton and Container Label
28 Oct 2008	Received HHS letter re: Anti-Infective Drug Advisory Committee
30 Oct 2008	Submitted response re: Request for Information
31 Oct 2008	Received FDA emails re: posting of Advisory Meeting Briefing Materials and Consultants
13 Nov 2008	Received FDA email re: Advisory Committee Meeting
18 Nov 2008	FDA Advisory Committee Meeting
11 Dec 2008	FDA Teleconference
20 Feb 2009	Received FDA Complete Response Letter
13 Mar 2009	Submitted response re: Complete Response Letter
20 Mar 2009	Submitted updated SPL File
16 Apr 2009	Received FDA email re: PPI for Telavancin
17 Apr 2009	Received FDA letter re: Receipt of NDA Resubmission
05 May 2009	Submitted response re: FDA Comments on Proposed PPI
05 May 2009	Submitted Drug Product Shelf Life Extension
13 May 2009	Submitted Patent Information

Date	Brief Description of Activities
15 May 2009	Received FDA email re: Labeling Comments
27 May 2009	Received FDA email re: request for information for REMS
29 May 2009	Submitted response re: Reviewer Comments
01 Jun 2009	Submitted response re: Reviewer Comments (revised)
10 Jun 2009	Submitted Patent Information
12 Jun 2009	Submitted response re: REMS Comments and Information Requests
22 Jun 2009	Received FDA email re: FDA Draft Label and Med-Guide
24 Jun 2009	Received FDA email re: REMS
01 Jul 2009	Received FDA email re: Recommendations for Pregnancy Exposure Registry Protocol
06 Jul 2009	Submitted response re: Proposed Labeling
13 Jul 2009	Submitted response re: Clinical/ Statistical Review Comments
13 Jul 2009	Submitted Labels
13 Jul 2009	Received FDA email re: Clinical-Statistical Review Team
16 Jul 2009	Submitted response re: Proposed Pregnancy Registry Protocol
16 Jul 2009	Received FDA email re: REMS Document Comments
27 Jul 2009	Submitted Label Content Rationale
27 Jul 2009	Received FDA email re: FDA Version of VIBATIV Label & Rationale Document
27 Jul 2009	Received FDA email re: Med-Guide and DHCP letter
28 Jul 2009	Submitted Revised Label
29 Jul 2009	Submitted Proposed Label
30 Jul 2009	Submitted response re: Comments on REMS
05 Aug 2009	Received FDA email re: request for information from Clinical/ Statistical Review Team
06 Aug 2009	Received FDA email re: Carton and Container Comments
07 Aug 2009	Submitted response re: request for information from Clinical/ Statistical Review Team
10 Aug 2009	Received FDA email re: VIBATIV Pregnancy Registry Protocol
11 Aug 2009	Received FDA email re: Carton and Container Comments

Date	Brief Description of Activities
12 Aug 2009	Submitted response re: Comments on REMS
13 Aug 2009	Received FDA email re: REMS Review
17 Aug 2009	Submitted response re: Comments on REMS
17 Aug 2009	Received FDA email re: Post-Marketing Requirements/ Commitments (PMR/PMC)
18 Aug 2009	Submitted revised response re: Comments on REMS
20 Aug 2009	Received FDA email re: Proposed PMR/PMC and Proposed Label
21 Aug 2009	Received FDA email re: PMC Document and Proposed Label
26 Aug 2009	Submitted response re: Proposed Label and Proposed Post-Marketing Commitment
27 Aug 2009	Received FDA email re: Proposed Label
27 Aug 2009	Received FDA email re: Proposed PMC
28 Aug 2009	Submitted response re: Proposed Label and Request for Confirmation of Fulfillment Dates for Post-Marketing Commitments and for Implementation of a Pregnancy Registry
28 Aug 2009	Submitted response re: Proposed Post-Marketing Commitments/ Requirements
28 Aug 2009	Received FDA email re: PMC/PMR Date Verifications
01 Sep 2009	Submitted correction re: Label
01 Sep 2009	Received FDA email re: Proposed Label
02 Sep 2009	Received FDA email re: REMS
02 Sep 2009	Received FDA email re: Label Correction
03 Sep 2009	Submitted response re: Proposed Label and Response to Proposed REMS Document
03 Sep 2009	Submitted revised response re: Proposed REMS Document
03 Sep 2009	Received FDA email re: Proposed REMS document
11 Sep 2009	Received FDA Approval Letter for NDA 22-110